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INDEX VOL. 49 FASC. 1

INDEX VOL 49 FASC 2

INDEX

VOL. 49 FASC. 3

(Cont. from cover pag 2)

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INDEX

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INDEX

VOL. 49 FASC. 4

INDEX

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INDEX

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From the Medical Department Central Hospital Karlskrona and the University Eye Clinic Lund

SARCOIDOSIS WITH OCULAR AND HYPOTHALAMIC – PITUITARY MANIFESTATIONS

BY

RAGNAR INGESTAD and GÖRAN STIGMAR

Generalized sarcoidosis causes a wide varity of systemic disorders in which ocular manifestations occur with a frequency of 25 % to 50 % (4 15 23) and an involvement of the central nervous system (CNS) occurs with a frequency of 1 % to 5 % (3 12 28 30 34) The pituitary hypothalamic region is one of the most common sites for CNS sarcoidosis with diabetes insipidus as the most com mon symptom (28)

Among the ocular manifestations in cases with CNS sarcoidosis those attri butable to a direct infiltration or indirect compression of the optic nerve are of special importance It is extremely rare however that a sarcoid granuloma – as in the present case – is situated in the optic disc thereby permitting an *in vivo* study of the development of a sarcoid lesion in a tissue of central nervous origin.

Case report

A 26 year old man who in March 1969 suddenly developed blurred vision in R. E was found to have papilloedema The right visual field was constricted and there was a paracentral scotoma L. E. was normal Visual acuity was 0 1 R E 1 0 L E A pre liminary diagnosis of non specific papillitis was made and on treatment with 20 mg prednisolone daily vision improved to 0 8 One month after the onset of symptoms he was admitted to the University Eye Clinic in Lund because of further protrusion of the oedematous optic disc from 3 to 5 diopters Examination of the right eye now revealed

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a visual acuity of 0 7 and a fine aqueous flare and small opacities in the vitreous body The right optic disc was found to be involved by a cauliflower like tumour projecting 6 diopters into the vitreous body It was gray in colour nodular and covered with a net of fine vessels some of them with small ectatic bulges There was a slight venous congestion but there were no haemorrhages The base of the tumour was approximately 2 times larger than a normal disc and was surrounded by oedema which also involved the macula A few yellow spots were seen along some of the arteries similar spots being found in the left eye The left optic disc was normal

Laboratory examination revealed a normal E. S R and normal serum electrolytes. Serum electrophoresis disclosed an increased gamma globulin fraction A spinal tap gave CSF at normal pressure containing 9 mononuclear cells per cubic mm and 46 mg protein per 100 cc electrophoresis being normal

Chest X ray examination showed a bilateral hilar lymphadenopathy a slight parenchymal process in the middle lobe and diffuse interstitial linear infiltrates in the lungs (Fig 3) Scalene fat pad biopsy was normal and pulmonary biopsy revealed a non characteristic fibrosis Mantoux (1 mg) was negative.

In spite of the negative biopsies the chest radiograph the negative Mantoux and the ophthalmological findings were highly suggestive of sarcoidosis The steroid treatment was stopped a few days before the diagnosis was verified Now the retinal oedema in the right eye increased and patches of exudates involved the macula The left optic disc became slightly oedematous (Fig 1)

Steroid treatment was reinstituted (30 mg prednisolone a day) About 7 weeks later a regression of the X ray findings was noted The optic tumour now protruded 8 diopters and the surrounding retina was folded The papilloedema of the left eye had disappeared as well as the vascular changes The steroids were reduced to 10 mg a day Five months after the onset small haemorrhages and white exudates appeared around the tumour and in the periphery the small vessels were sheathed (Fig 2) The vision was now reduced to finger counting and 10 months after the onset of the disease the eye was amaurotic The tumour was grayish white in colour and protruded more than 12 diopters Steroid treatment had been continued but reduced to 5 mg a day After 14 months there still were haemorrhages but the exudates were arranged in concentric circles around the tumour and extended even out to the periphery of the fundus The steroid treatment was stopped In the course of the following 6 months numerous dense spots appeared in the posterior vitreous membrane which formed a funnel like detachment The general condition of the patient was good and there were no signs of neurological manifestations of sarcoidosis during this first period of the disease

In February 1967 the patient experienced increased thirst drinking 5 to 6 litres a day From May 1967 varying swelling of the parotid glands was observed but no neurological changes except the ocular changes of the right eye could be observed In August 1967 a general physical examination revealed no signs of hypogonadismus parotid swelling or fever Scalene node biopsy revealed epitheloid cell granulomatosis without caseation – sarcoid lesions Roentgenological examination of the cranium including the sella gave a normal result but there was a progress of the pulmonary changes (Figs 4 5) The patient had a diuresis of more than 8 litres a day no glycosuria or proteinuria being observed

The diagnosis of diabetes insipidus was verified as follows After water deprivation for 12 hours the urine volume was 180 cc hour and the urine osmolality 187 mOsm kg The ratio of urine to plasma osmolality was 0 6 Thus it was demonstrated that the patient could not respond normally to the water deprivation Aqueous vasopressin 0 5 unit then was given intravenously whereupon the urine volume rapidly was reduced to

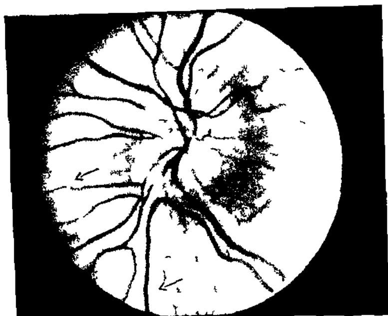


Fig 1
Left fundus showing a slight papilloedema and a few candlewax drops
(1 month after the onset)

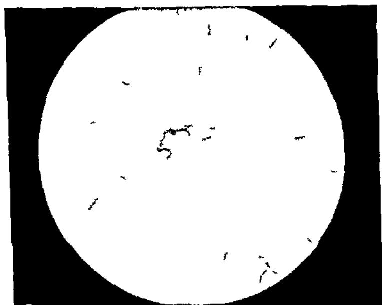


Fig 9
Right fundus with the cauliflower like sarcoid granuloma of the optic nerve surrounded by patches of exudates and haemorrhages in the oedematous retina
(5 months after the onset)



Fig 3
Moderate bilateral hilar lymph node enlargement Parenchymatous changes of miliary type in both lungs more pronounced on the right side (1965)

37 cc/hour and the urine osmolality was increased to 440 mOsm/kg The ratio of urine to plasma osmolality arose to 1 4

The fasting blood sugar was normal but glycose loading test showed a maximum value of 0 18 g % The E S R was about 30 mm/hour Serum electrophoresis showed a diffuse gammaglobulin increase (2 0 g %)

Parenteral treatment with Pitressin Tannate in Oil (Parke Davis) 5 IE a day immediately reduced the polyuria the urine quantities becoming less than 2 litres a day Prednisolone treatment (20 mg daily) was started

In September 1967 the patient was in good condition He had no polyuria and the E S R had become normal Accordingly the prednisolone treatment was gradually decreased and by the simultaneous administration of polythiazide (Renese® Pfizer) 1 mg a day the pitressin treatment could be reduced to 2–3 days a week

In May 1969 pitressin was exchanged for chlorpropamide (Diabenes®) 0 75 gram a day while the polythiazide treatment was continued No signs of hypoglycemia could be observed Gradually the chlorpropamide dose could be reduced to 0 25 gram daily with continued good effect on the diabetes insipidus At the present time the patient is being treated with prednisolone 5 mg and chlorpropamide 0 50 gram a day Polythiazide has been eliminated



Fig 4
The previously described findings have progressed to form larger nodules (1967)

Summary of case report

A 26 year old man had a tumor of the optic disc interpreted as a sarcoid granuloma posterior uveitis bilateral hilar lymphadenopathy and disseminated changes in the pulmonary parenchyma Two years later a bilateral parotid swelling developed and a diabetes insipidus attributable to a lesion of the pituitary hypothalamic region The multiple signs of a systemic involvement the negative tuberculin test the hypergammaglobulinemia the histopathology of a biopsy proved the diagnosis of generalized sarcoidosis

Discussion

In sarcoidosis any part of the nervous system may be involved The most frequent finding is involvement of the basal leptomeninges with granulomatous and adhesive changes (24) The usual result of a basal engagement is cranial



Fig 8
Moderate bilateral hilar lymph node enlargement Parenchymatous changes of miliary type in both lungs more pronounced on the right side (1965)

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Lesions of a large granulomatous type are sometimes sufficiently distinctive to allow an almost certain diagnosis Smaller lesions situated near the vessels and characterised as candle wax drops are considered to be pathognomonic for the disease (2 8) A perivascular sheathing (periphlebitis) is a less distinctive clinical finding as is also the chorioretinitis

The eye symptoms in this case were bilateral and restricted to the posterior segment of the eye except for a fine aqveous flare The vascular changes with the candle wax drops in the acute phase of the disease seemed to be sensitive to the steroid treatment and disappeared after about one month leaving no scars On the contrary the vitreous changes have gradually increased These opacities on the posterior vitreous membrane are now dense enough to prohibit a thorough examination of the fundus According to Duke Elder they were first described by Landers (?0) and they may be a characteristic feature of ocular sarcoidosis but not a pathognomonic one (5)

The lesions of the optic nerve are of special interest and in systemic sarcoidosis they may develop under the following circumstances

1 Papilloedema secondary to a posterior uveitis (papillitis) The most common cause of papilloedema in sarcoidosis and probably the explanation of the slight papilloedema in the present case Rapid regression is often noted with cortisone treatment

2 Papilloedema (choked disc) as an expression of increased intracranial pressure when the primary lesion is situated in CNS or as a consequense of a chronic reaction of the basal leptomeninges In the latter case cortisone treatment can be of value (2)

3 With a clinical picture of optic neuritis (retrobulbar neuritis) with a central scotoma in the visual field Treatment with systemic steroids or ACTH is reported to give excellent results in some of these cases (6) but some pass into an optic atrophy (17)

4 Optic atrophy secondary to compression or infiltration from a primary focus in CNS (19 29 35) Bitemporal defects of the visual fields due to suprasellar involvement are reported (3 38)

5 Primary granuloma of the optic nerve In many cases there will be difficulties in differentiating between cases belonging to group 4 and 5 respectively

In the present case two years had passed before any signs of symptoms developed which could be attributable to an involvement of CNS thus it seems justifiable to rank this case in group 5

In 1931 Reis & Rothfeld (29) reported a case with bilateral optic involvement and in recent years another three cases have been described (21 26 32) In one of these cases (21) the tumor disappeared without treatment In another case (26) with a picture much like the Heerfordt syndrome a slight but transistory regression was noted on treatment with ACTH but the final result was an optic atrophy



Fig 5
Marked progress with coarse granular pattern and patchy infiltrates in the right lung (1969)

nerve involvement especially the facial optic and oculomotor nerves (3 12) A direct invasion of the brain from the subarachnoidal space is not unusual Lesions often are found in the pituitary – hypothalamic region (3 11 12 13 27 28 30 31 33 36 38)

Colover (3) reported 20 cases of sarcoidosis with polyuria and polydipsia and several with hypersomnia and lethargia obesity hypogonadismus amenorrhea bitemporal hemianopsia and enlarged sella turcica all indicating hypothalamic – pituitary involvement

Eye manifestations are reported to be the third or fourth most common localization of systemic sarcoidosis (5 16) Almost every structure of the eye can be affected but the occurence of lesions in the posterior segment is relatively rare (5) Approximately 10 per cent of all eye manifestations are restricted to the posterior pole (4 10 16)

The *ophthalmoscopic examination may present a great variety of features*

Lesions of a large granulomatous type are sometimes sufficiently distinctive to allow an almost certain diagnosis Smaller lesions situated near the vessels and characterised as candle wax drops are considered to be pathognomonic for the disease (2 8) A perivascular sheathing (periphlebitis) is a less distinctive clinical finding as is also the chorioretinitis

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The treatment of central nervous system sarcoidosis is usually not satisfactory Magnus (22) treated two cases of sarcoidosis involving the hypophysis with ACTH and cortisone There was improvement of the systemic manifestations but no objective evidence of improvement in the endocrine function was pre sented Selenknow et al (31) reported a case of hypopituitarism due to hypo thalamic sarcoidosis and prednisolone failed to alter the clinical course Suc cessful treatment of CNS sarcoidosis with steroids is however reported (7 25 33)

Specific treatment of diabetes insipidus with pitressin may not be required if polyuria and thirst not are too severe Thiazide diuretics (14 18 37) and chlor propamide (1 9 13 37) may produce diminution in polyuria and polydipsia and thus be useful in the treatment of diabetes insipidus

The therapeutic response by steroid treatment was in the case reported varying as regards the ocular manifestations The prednisolon therapy seemed to be of great value initially on the vascular changes and on the papilloedema and when this drug was withheld a few days to confirm the diagnosis there was a rapid progression In spite of full steroid treatment however it was not pos sible to prevent the development of a massive granuloma of the optic papilla which finally resulted in amaurosis of that eye

The diabetes insipidus did not regress during the steroid treatment but pitres sin had an excellent effect The pitressin quantity could be reduced when poly thiazide was supplied Then the pitressin and polythiazide treatment could be exchanged for chlorpropamide

Summary

A case of histologically verified generalized sarcoidosis with ocular and hypo thalamic pituitary involvement is presented The site of a sarcoid granuloma on *the optic papilla made it possible to study the development of sarcoid lesions in* detail An effort has been made to classify the different types of optic nerve in volvement which may occur in sarcoidosis and to make an evaluation of the effect of steroids on the different sarcoid manifestations The therapeutic response of the diabetes insipidus to chlorpropamide is emphasized

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Fig 1
Postoperative appearance

Maumenee & Shannon[6] (1956) e g found epithelial downgrowth in 18 % of 75 cases of eyes enucleated following cataract extraction Of 192 enucleated eyes collected through twenty five years *Eldrup Jorgensen*[3] (1969) found an inci dence of 8 % but the incidence in the last half of the period was twice that of the first a tendency that other authors have also noticed (*Sullivan*[9] 1957)

The reason for this is possibly to be found in an altered surgical technique cataract extractions e g were previously extracapsular with only a suturation of conjunctiva in the ab externo incision whereas they are now intracapsular extractions with suturation of the nearly 180° wide corneoscleral incision. How ever *Eldrup Jorgensen*[3] points out furthermore that the patient material has changed during recent years cataract extractions are performed on older pa tients than previously and in many more complicated cases One of the patients from the latter half of the period had diabetes mellitus just like the patient re ferred to here Nearly all authors point out improper closure of the wound to gether with slow healing delayed formation of the anterior chamber and hypo tonia as predisponent factors to epithelial downgrowth Too deeply placed stit ches incarceration of the iris or capsular remnant in the wound are particularly considered as openings for epithelial invasion

In 1937 *Perera*[7] differentiated three types of epithelial invasion of the ante rior chamber *Epithelial pearls epithelial cysts* and *epitheli ation* of the anterior chamber Histologically they are difficult to separate but the clinical course varies greatly (*Maumenee & Shannon*[6])

In some cases the diagnosis is difficult and can only be made by a histologic examination of a small scraping of the membrane on the posterior surface of the cornea (*Calhoun*[2] 1966)

Maumenee[4] has listed the following possibilities of misdiagnosing 1) A very

The purpose of this report is to describe a case of epithelial downgrowth into the anterior chamber successfully treated according to Maumenee s method

Case History

(E L 180805) 49 year old male with diabetes mellitus found a year before Well regulated on 1 tablet Arcosal daily

October 1967 Cataract extraction on the right eye Corneal Graefe incision cryoextraction through round pupil after peripheral iridotomy and zonulolysis with chymotrypsin The wound was closed with five 6-0 chromic catgut without conjunctival cover injection of air into the chamber The operation and the postoperative course were uneventful the chamber remained deep from the first day and there was no prolapse of the iris or the vitreous When discharged from hospital the patient suffered no wound insufficiency and there was only a mild uveitic reaction

Five weeks after the operation a thin membrane was detected on the superior temporal region of the posterior surface of the cornea limited downward by a slightly curved fine greyish line There was no inflammatory reaction of the eye the chamber was deep a snip of the iris adhered temporal to the cicatrix Visual acuity 0 4

Quite slowly the membrane on the posterior surface of the cornea grew in a broad tongue A few months later it had spread slightly down into the area of the pupil and then the growth stopped Approximately 2 months after the operation the pupil was found to be drawn slightly up toward the temple and a fortnight later a thin film on the hyaloid membrane could be seen in the superior pupillary region Here it continued to grow after the membrane on the posterior surface of the cornea had stopped spreading and after four months it covered half of the pupil There was some superficial and deep vascular growth in the superior region of the cornea and gradually uveitic reaction occurred becoming more and more painful which could not be affected by steroid treatment Tension varied from 10-17 mm Hg

Four months after the cataract extraction the patient was reoperated according to Maumenee s method At the same time as the wide iridectomy was undertaken the membrane in the pupillary region was easily removed without any loss of vitreous The wound was closed with silksutures and covered with conjunctiva There was no pain after the operation and only a moderate inflammatory reaction Corresponding to the treated part a dense milky obscurity developed in the cornea quite sharply demarcated against the clear cornea in which was seen a few vertical folds in Descemet s membrane

Nineteen months later there was no inflammatory reaction of the eye and no evidence of recurrence (Fig 1) Visual acuity 0 5 Tension approximately 20 mm Hg Normal ophthalmoscopy with no signs of diabetic retinopathy

Discussion

As already mentioned epithelial downgrowth into the anterior chamber following cataract extraction is rare *Theobald & Haas*[9] (1948) found an incidence of 0 11 % in a material of 8062 cataract extractions Epithelial invasion however accounts for a considerable part of the complications that result in enucleation

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shelving corneal incision 2) vitreous in contact with the posterior surface of cornea 3) invasion of the anterior chamber by connective tissue and blood vessels 4) a peeling off of Descemet s membrane from the posterior surface of the cornea and 5) a glassy membrane on the posterior surface of the cornea and the iris However only the latter of these lesions which is caused by ruptures in Descement s membrane and consists of a reduplication or a proliferation of Descemet s membrane may involve the anterior surface of the iris in the process

If the diagnosis is certain from the clinical examination or has been ascertained through a biopsy it is *Maumenee s* opinion that the surgical treatment suggested by him is indicated if the membrane does not affect more than one third of the anterior chamber Cases of more wide spread epithelial downgrowth or cases complicated by glaucoma are hardly suitable

In the present case the operation was uneventful and the postoperative course also surprisingly steady with no pains despite the fact that the operation must be regarded as being very traumatic. According to *Sullivan*[5] the operation is also usually followed by a loss of vitreous and often made difficult by profuse bleeding from the scleral wound There can also be considerable intermittent pains for some weeks after the operation

Scarification of the treated part of the cornea is unavoidable which is a vital reason for the mentioned restriction in the use of this method

Summary

An account is given of a case of epithelization of the anterior chamber following uncomplicated cataract extraction successfully operated according to Maumenee s method The patient was a 49 year old male with mild diabetes mellitus The postoperative follow up lasted 42 months The eye retained a visual acuity of 0 5

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The flat preparation technique for study of the vasculature and myelinated nerves of the iris was described in an earlier work (Saari 1970) The purpose of the present investigation was to throw light on the possibility of employing trypsin digestion and melanin bleaching of the iris for studying the vasculature and myelinated nerves of the pig iris

Material and Methods

Fresh pig eyes from an abattoir were used The number of eyes examined was 144

Fixation The eyes were mainly fixed in neutral formalin the iris was dissected free and washed in distilled water as described in an earlier study (Saari 1970) For control purposes seven irises were used fresh without fixation

Digestion time To demonstrate the vasculature and innervation of the pig iris the digestion time was determined as follows The irises were incubated at 37°C in a solution of 3 per cent trypsin (Difco 1 250) and 0 1 M tris buffer (pH 7 8) for one hour–12 days (Fig 1) When the incubation time was longer than 24 hours the trypsin tris buffer solution was changed twice per 24 hours The preparation was washed in distilled water The melanin of the iris was bleached as described earlier (Saari 1970) After rinsing with distilled water

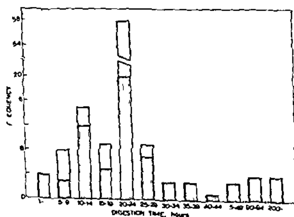


Fig 1
Distribution of digested and bleached irises according to the digestion time Shaded columns Irises stained with PAS hematoxylin

From the Eye Clinic University of Helsinki
(Head Professor Salme Vannas M D)

TRYPSIN DIGESTION AND BLEACHING FOR STUDYING THE VASCULATURE AND MYELINATED NERVES OF THE PIG IRIS

BY

MATTI SAARI

Kuwabara and Cogan succeeded in 1960 in separating the vascular net of the retina by digesting the nonvascular components of the retina in trypsin solution The same method has since been widely used to study the retinal vasculature (Cogan Toussaint & Kuwabara 1961 Toussaint Kuwabara & Cogan 1961 Kuwabara Carrol & Cogan 1961 Wolter 1961 a Wolter 1961 b Wolter 1962 Cogan 1962 Toussaint Cogan & Kuwabara 1962 Reinecke Kuwabara Cogan & Weis 1962 Cogan 1963 Mutlu & Leopold 1964 Sugi 1966 Hyvarinen 1967)

The vasculature of the choroid has been studied in flat preparations by the trypsin digestion technique (Friedman Smith & Kuwabara 1963 Ring & Fujino 1967) Trypsin digestion was not combined with melanin bleaching in these studies Instead trypsin digestion was combined with vigorous shaking of the preparation for a period of 30 to 90 minutes with a maximum setting of 260 excursions per minute The thickness and density of pigmentation of some preparations made it advantageous to dissect off a portion of the large vessel layer These studies were concerned only with the vascularisation of the choroid, not with its innervation

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Authors adress
Universitetscentralsjukhuset Ögonkliniken Haartmansgatan 4 C
Helsingfors 29 Finland

Table 1

Number of irises stained with different techniques after trypsin digestion and bleaching and the digestion times

Staining method	Digestion time (hours)	Irises
PAS hematoxylin	20	17
Mallory's aniline blue	20	19
Alcian blue	16	4
	20	8
Van Gieson	20	6
Hematoxylin eosin	24–30	9

Results

Fixation Neutral formalin lends itself well to fixation when trypsin digestion is used Fresh unfixed irises are also very suitable for the trypsin digestion technique

Effect of trypsin digestion without bleaching on the visualisation of vessels and nerves in a preparation stained with PAS hematoxylin Chromatophores tolerated trypsin digestion for a long time in irises stained after digestion times of varying lengths without bleaching After 48 hours of trypsin digestion chromatophores were still abundant in the preparation and obscured demonstration of the vasculature and nerves in a flat mount preparation (Fig 3 a) Disintegration of the chromatophores and dispersal of pigment granules in the preparation was more marked after 72 hours of trypsin digestion (Fig 3 b) Melanin tolerated digestion long after the nuclei and cytoplasm of the pigment cells had disintegrated (Fig 3 c) Trypsin digestion failed to bring out either blood vessels or nerves in unbleached PAS hematoxylin stained flat preparations of the pig iris

Trypsin digestion and bleaching Quarters of the same iris were compared the first stained with PAS hematoxylin (Fig 4 a) the second bleached and stained with PAS hematoxylin (Fig 4 b) the third stained with PAS hematoxylin after 20 hour trypsin digestion (Fig 4 c) and the fourth stained with PAS hematoxylin after 20 hour trypsin digestion and bleaching (Fig 4 d) Both unbleached preparations contained a great many chromatophores The unbleached quarter subjected to 20 hour trypsin digestion was thinner but neither vasculature nor innervation was visualised Blood vessels and myelinated nerves were demonstrable in the bleached preparations and the quarter of the iris that had been subjected to 20 hour trypsin digestion was distinctly

the preparation as a whole was floated on a slide or after halving the two halves on different slides dried and stained by different techniques

Effect of trypsin digestion without bleaching The object was to establish whether it is possible to demonstrate the vasculature and innervation of the pig iris by trypsin digestion without bleaching

a) Twenty irises were examined after digestion times of varying duration without bleaching with PAS hematoxylin or after halving one half was stained without bleaching with PAS hematoxylin and the other half was stained after bleaching with PAS hematoxylin (Fig 2)

b) Five eyes were examined as follows The iris was divided into four the 1st quarter without digestion and bleaching the 2nd bleached without digestion the 3rd after 20 hours trypsin digestion unbleached and the 4th after 20 hours trypsin digestion bleached was stained with PAS hematoxylin

Staining Several staining methods were tried to achieve better visualisation of the vessels and myelinated nerves After digestion and potassium permanganate bleaching the preparation was stained with PAS hematoxylin Mallory s aniline blue the van Gieson technique Alcian blue (ICI) or hematoxylin eosin (Table 1)

Thinning of the preparation Six irises were studied in the following manner The preparation was digested for five hours in trypsin solution bleached with potassium permanganate and floated on a slide The anterior stroma was dissected off with small scissors under the dissecting microscope The preparation was dried and stained with PAS hematoxylin

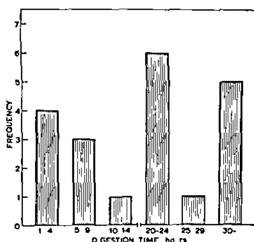


Fig 2

Distribution of digested unbleached irises stained with PAS hematoxylin according to the digestion time



Fig 5c

thinner and the myelinated nerves were visualised clearly better in it than in the undigested quarter Trypsin digestion by itself did not bring out the vasculature and myelinated nerves in the flat preparation stained with PAS hematoxylin On the other hand the vasculature and myelinated nerves were best visualised when trypsin digestion and bleaching of the melanin of the iris were combined

Digestion time The incubation time of trypsin digestion in this study was long The preparation had thinned enough in four hours to keep on the slide during the staining procedure Examination of the preparation stained with PAS hematoxylin after bleaching revealed that the vasculature and myelinated nerves were visualised satisfactorily only after 13 hour trypsin digestion (Fig 5) When the incubation time was prolonged digestion of the stroma continued and this could be seen as fainter staining of the background and clearer visualisation of the myelinated nerves After 20 hours of trypsin digestion the background stained evenly and thinly the myelinated nerves emerged beautifully and it was possible to follow them from an individual fibre with myelin sheath in the sphincteric region to the long posterior ciliary nerve Blood vessels were also visualised but they stained paler The capillary network was not visualised (Fig 6)

When the incubation time was prolonged the preparation thinned further



a



b

Fig 3

Unbleached PAS hematoxylin stained flat preparation of the pig iris Vasculature and innervation not visualised – a Trypsin digested for 48 hours Numerous chromatophores visible × 320 – b Trypsin digested for 72 hours The chromatophores show disintegration and release of pigment into the preparation × 350 – c Trypsin digested for 144 hours The chromatophores have disintegrated further × 350



Fig. 4c. Flat preparation. Quarter of the same iris that has been digested for 90 hours. The preparation is thinner than the unbleached and undigested quarter of the iris. Chromatophores are still visible, neither vasculature nor innervation is visualised. PAS hematoxylin × 80

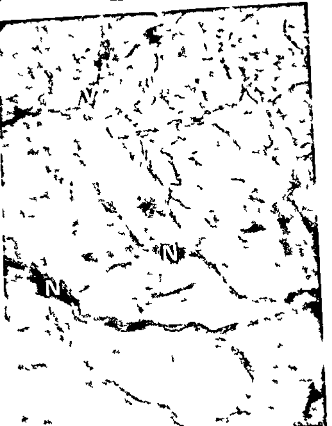


Fig. 4d. Flat preparation. Quarter of the same iris that has been digested for 0 hours and bleached. Myelinated nerves (N) are well visualised. Blood vessels (V) are faintly visible. The background is considerably thinner than in the bleached undigested iris quarter. PAS hematoxylin × 80

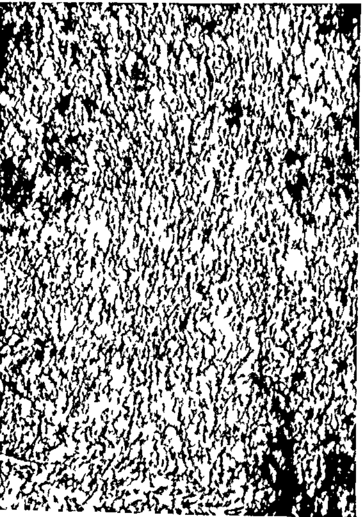


Fig 4 a Flat preparation Unbleached and undigested quarter of pig iris Numerous *chromatophores are visible Neither* vasculature nor innervation is visualised PAS hematoxylin × 80

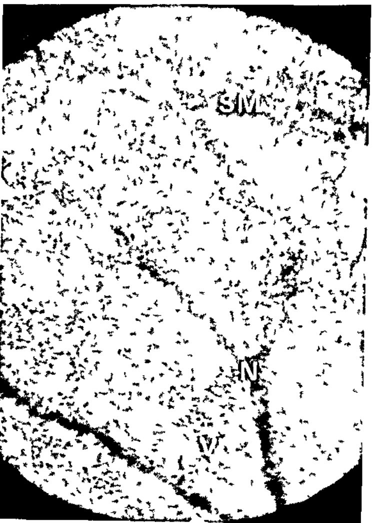


Fig 4 b Flat preparation Bleached quarter of the same iris Myelinated nerves (N) are visualised radial blood vessels (V) are less faint The sphincter muscle (SM) is clearly visible PAS hematoxylin × 80

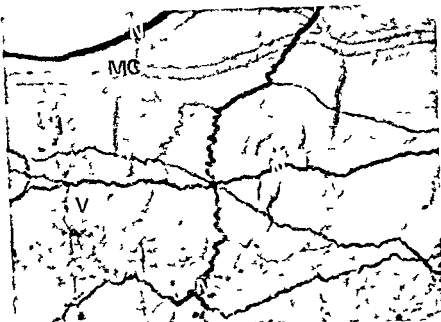


Fig 6

Flat preparation Pig iris that has been digested for 20 hours with trypsin and bleached The major arterial circle of the iris (MC) and the radial vessels (V) are visible Myelinated nerves (N) are visualised well PAS hematoxylin × 32

When the digestion time was prolonged the preparation began to swell After 284 hour trypsin digestion and bleaching the preparation was thick and curled into a roll It was difficult to spread on the slide PAS hematoxylin staining revealed heavy staining of the background Remains of myelinated nerves were seen in the heavily digested preparation (Fig 9)

Twenty hours proved to be the best duration of trypsin digestion for visualisation of the vasculature and myelinated nerves on a flat preparation of the pig iris after trypsin digestion bleaching and PAS hematoxylin staining (Fig 10)

Thinned preparation Blood vessels myelinated nerves and muscle fibres were clearly demonstrable in a flat preparation which was thinned after 5 hour trypsin digestion and potassium permanganate bleaching and stained with PAS hematoxylin The structure of the blood vessel walls was visualised better than in an unthinned preparation digested for 20 hours bleached and PAS hematoxylin stained

Different staining methods The myelinated nerves in a trypsin digested and

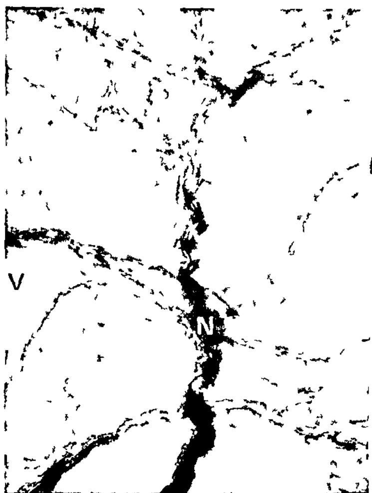


Fig 5

Flat preparation Pig iris that has been digested for 13 hours with trypsin and bleached Myelinated nerves (N) are visualised well Blood vessels (V) stain pale The background is fairly well thinned PAS hematoxylin × 80

but the myelinated nerves were no better visualised than in the flat preparation digested for 20 hours After 30 hours of trypsin digestion the background began to stain more heavily in the pupillary part where more darkly stained places were seen After 35 37 hours of trypsin digestion more densely staining places appeared also in the ciliary part The blood vessels were no longer distinct but nerves with a myelin sheath still emerged well (Fig 7) Myelinated nerves were still visible in a bleached preparation stained with PAS hematoxylin after 91 hours of trypsin digestion But the blood vessels were no longer distinguishable from the background (Fig 8) The sphincter muscle was still visualised in the flat preparation of the pig iris which was digested for 91 hours, bleached and stained with PAS hematoxylin

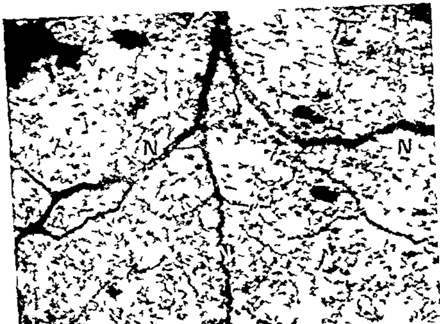


Fig 8

Flat preparation Pig iris that has been digested for 91 hours and bleached The myelinated nerves (N) are still visualised well PAS hematoxylin × 37

Discussion

Melanin resists trypsin digestion for a long time (Lillie 1954) This appeared clearly also in the present study in which chromatophores were found after 72 hour digestion obscured visualisation of the blood vessels and nerves in a flat mount preparation of the pig iris Abundant melanin pigment released from chromatophores was seen in the preparation after 144 hours of trypsin digestion Therefore in addition to trypsin digestion bleaching of melanin must also be performed The human choroid is thinner and can actually be demonstrated after 15 30 min digestion and shaking for 30–90 min without bleaching the choroidal vasculature (Friedman Smith & Kuwabara 1963)

The digestion time for the retina is short 1–3 hours (Kuwabara & Cogan 1960) The optimal digestion time for demonstration of the vasculature and myelinated nerves in pig iris was long 20 hours The stroma of the pig iris is thick If the anterior part of the stroma is cut off and the PAS hematoxylin staining technique is used the structure of the walls of the iris vessels can be better visualised after 5 hour trypsin digestion and potassium permanganate bleaching It has been pointed out in regard to retinal trypsin digestion that



Fig 7

Flat preparation Pig iris that has been digested for 37 hours with trypsin and bleached The ciliary part shows numerous intensely stained places (arrows) The myelinated nerves (N) are still visualised well PAS hematoxylin × 32

bleached flat preparation of the pig iris were dark purple on PAS staining The blood vessels stained a pale colour With hematoxylin eosin the flat mount preparation stained an even pale colour and neither the blood vessels nor nerves were demonstrated Hematoxylin stained only the nuclei blue and eosin failed to bring out either the vessels or nerves Hematoxylin eosin however sometimes revealed capillaries on the thinner pupillary margin

The myelinated nerves stained a clear blue with Alcian blue With van Gieson s technique the collagen in the background stained red and the muscle fibres yellow The preparation gave a uniform orange impression and neither the blood vessels nor the nerves were visualised Mallory s aniline blue stained the background a very intense dark colour and brought out neither the vasculature nor the innervation in a flat mount preparation of the pig iris

Comparison of different staining methods showed the superiority of PAS hematoxylin staining for studying the vasculature and myelinated nerves of a digested and bleached flat preparation of the pig iris The results of the different staining methods are presented in Table 2



Fig 8
Flat preparation Pig iris that has been digested for 91 hours and bleached The myelinated nerves (N) are still visualised well PAS hematoxylin × 32

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vascular components of the iris in a solution of trypsin Interestingly in a flat preparation of the pig iris myelinated nerves showed up well with PAS hematoxylin staining after 20 hour trypsin digestion and potassium permanganate bleaching

The major retinal arteries stained an intense red with PAS staining after trypsin digestion of the retina the veins were equally distinct but stained less intensely (Kuwabara & Cogan 1960) The blood vessels stained a pale purple in a flat preparation of the pig iris after trypsin digestion and potassium permanganate bleaching The myelinated nerves stained a dark purple

The adventitia of the iris vessels stain well with Alcian blue in serial sections whereas the stroma stains considerably more faintly (Rohen 1964) Alcian blue staining brings out well the myelinated nerves in a flat preparation of the pig iris after trypsin digestion and bleaching

To study the innervation of the uveal tract Castro Correia (1967) used Schabadasch s methylene blue technique as modified by Hillarp (1946) and the ammoniated silver carbonate technique (Jabonero 1948) Cholinergic innervation has been demonstrated by the thiocoline method (Koelle & Friedenwald 1949) and by a simplified modification (Gomori 1952)

Catecholamines form intensely fluorescent compounds when treated with formaldehyde A method for the histochemical demonstration of norepinephrine in the adrenal medulla based on this principle was reported by Eränko (1952 and 1955) Formaldehyde in vapour form was first employed for histochemical localisation of histamine in mast cells (Lagunoff Phillips & Benditt 1961) At about the same time the high sensitivity of the formaldehyde vapour technique for histochemical localisation of monoamines was demonstrated (Falck & Torp 1961 Eranko & Harkonen 1963 Eranko 1964) Application of the histofluorometric technique to nervous tissues (Falck 1962) has since proved fruitful in microscopic study of monoaminergic neurones and has also been used for demonstration of the adrenergic innervation of the iris

In studying cholinesterases monoamine oxidase and phosphorylase in the iris muscles of human and pig eyes (Niemi & Tarkkanen 1964) Gomori s method was used for determination of cholinesterases and monoamine oxidase activity was studied by the tryptamine tetrazolium method of Glenner et al (1957)

Combination of the formaldehyde vapour technique and the acetylcholinesterase method made it possible to extend the scope of comparative studies of aminergic and cholinergic structures (Eranko & Härkonen 1964 Eränko & Härkönen 1965 Eranko 1965) The same method has been used for studying the nerve net of the rat iris (Eranko & Raisanen 1965)

All these methods have their advantages and limitations In a flat preparation of the pig iris PAS hematoxylin staining brought out the myelinated nerves after potassium permanganate and oxalic acid bleaching (Saari 1970) In

the present study the myelinated nerves were visualised beautifully in a flat preparation of the pig iris after 20 hour trypsin digestion and potassium permanganate bleaching This method has the advantage of making it possible to study the innervation and vasculature at the same time It also enables histologic examination of complete blood vessels and myelinated nerves which can not be seen in serial sections of the iris Thus it seems to be a useful method for studying anatomical aspects and possibly even pathological changes of the iridic vasculature and innervation

Summary

The trypsin digestion and bleaching technique for studying the vasculature and myelinated nerves of the pig iris is described After enucleation the eye was fixed in 10 per cent neutral formalin for a minimum of 24 hours The eye was opened equatorially The vitreous and the lens were removed with forceps and scissors The iris ciliary body and anterior choroid were freed in toto The residue of the vitreous and the pigmentary layer of the iris were wiped of with pieces of blotting paper The ciliary process was cut away with small scissors The preparation was washed overnight in several changes of distilled water It was incubated at 37 C in a solution of 3 per cent trypsin (Difco 1 250) and 0 1 M tris buffer (ph 7 8) for 20 hours The preparation was washed in distilled water It was kept in 0 25 per cent potassium permanganate solution for four hours and washed in water kept in 5 per cent oxalic acid solution for six min and washed in distilled water The flat preparation was floated on a slide dried and stained with PAS hematoxylin

The method permitted simultaneous observation of the major arterial circle radial vessels and myelinated nerves of the pig iris The course and relations of the vessels and myelinated nerves were better illustrated than in serial sections

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From the Eye Clinic University of Helsinki
(Head Professor Salme Vannas M D)

OBSERVATIONS ON THE BLOOD VESSELS OF THE PIG IRIS

BY

MATTI SAARI

The trypsin digestion and bleaching method for studying the vasculature and myelinated nerves of the pig iris was described in an earlier paper (Saari 1971a) With this method the myelinated nerves stained dark purple and became distinctly visible Blood vessels stained pale purple but capillaries were not visualised The present paper reports on an injection digest bleaching method for study of the minute vasculature of the pig iris Different contrast media are compared

When contrast medium was injected into the long posterior ciliary artery or the vortex vein the course of the vessels appeared different from that earlier described (Zietzschmann 1906 Barth 1927 Prince Diesem Eglitis & Ruskell 1960) For this reason the course and structure of the central vessels of the pig iris will be described first The anterior ciliary arteries and the anterior ciliary venous system are not dealt with here however

Material and Methods

Fresh pig eyes from an abattoir were used The pigs were of Finnish cross breed females and castrated males aged 6–7 months and of 60 70 kg body weight

Macroscopic examination Ten pig eyes five right and five left which were not pairs were examined The temporal conjunctiva of the eye was marked with a pin A sharp knife was used to remove the eyelids the eyeball and as much of the orbital contents as possible *all in one piece The right eyes were placed in*

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one container and the left eyes in another Using a millimetre measure the distances were recorded between the optic nerve and the point where the long posterior ciliary artery reached the ocular surface in each of the eyes and also between the limbus and the point at which the long posterior ciliary artery pierced the sclera In addition measurements were made of the perpendicular distances along the surface of the sclera from the point of emergence of the vortex vein on the external surface of the sclera to the limbus and to the long posterior ciliary artery

Microscopic examination Nine pig eyes were examined Four eyes were fixed in 10 per cent neutral formalin and five eyes using Zenker s fixation Serial paraffin sections were cut at 5 to 8 microns Hematoxylin eosin PAS hematoxylin Weigert van Gieson Nassar s silver stain and myelin stain were used for paraffin sections

The injection digest bleaching method 83 pig eyes were examined Contrast medium was injected into the long posterior ciliary artery or vortex vein from a 2 cc plastic syringe attached to a 2R2 0 4–11 mm injection needle Ink was injected into 15 eyes Indian ink (Gunther Wagner Pelikan) into 15 eyes 5 per cent aqueous solution of Soluble Berlin blue into 22 eyes and Neoprene latex (Neoprene latex 572 coloured blue Neoprene latex 572 coloured red Du Pont Co Ltd Elastomers Research Laboratory) was injected into 10 eyes In 15 eyes Neoprene latex coloured red was injected into the long posterior ciliary artery and Neoprene latex coloured blue into the vortex vein

To facilitate injection illumination was provided by the light of the dissecting microscope (a 6 V 5 A Philips bulb 4–4 5 amperes) and operation glasses were used (Zeiss telescope lenses magnification 2 ×) The injected eyeball was fixed in 10 per cent neutral formalin for a minimum of 24 hours The iris was freed digested bleached and stained with PAS hematoxylin as described earlier (Saari 1970 b)

Paraffin sections were prepared from the posterior parts of three eyes after injection of 5 per cent aqueous solution of Soluble Berlin blue into the long posterior ciliary artery for the purpose of checking that the contrast medium really had entered the artery

Five irises were examined without previous injection after 20 hour trypsin digestion and potassium permanganate bleaching (Saari 1970 b) with Alcian blue (ICI) PAS hematoxylin staining

Results

A The course of the long posterior ciliary arteries and the vortex veins

The long posterior ciliary artery reaches the surface of the pig eye nasally and

temporally to the optic nerve Nasally its distance from the optic nerve is 5–13 mm and temporally 1–3 mm It passes along the scleral surface nasally in the horizontal meridian and temporally slightly lower, also horizontally Profuse pigment is seen around it *The long posterior ciliary artery pierces the sclera* nasally 10–15 mm and temporally 6–10 mm away from the limbus (Table 1)

The superior nasal vortex vein of the pig eye emerges from the eyeball at a distance of 10–15 mm from the limbus and 10–13 mm above the long posterior ciliary artery The inferior nasal vortex vein emerges from the eyeball at 10–12 mm from the limbus and 6–9 mm below the long posterior ciliary artery The point of emergence of the superior temporal vortex vein from the eyeball is 12–14 mm away from the limbus and 11–13 mm above the long posterior ciliary artery and that of the inferior temporal vortex vein 9–10 mm from the limbus and 7–9 *mm below the long posterior ciliary artery* (Table 1)

The long posterior ciliary artery runs in the orbit behind the eye accompani

Table 1

Distance measured from point where long posterior ciliary artery (l p c a) reaches ocular surface to optic nerve (a)

Distance measured from point where the artery pierces the sclera to limbus (b)

Distances to limbus (c) and to long posterior ciliary artery (d) respectively from the point of emergence of superior (sup v v) and inferior (inf v v) vortex veins

Distances in mm

Eye	Nasal side						Temporal side					
	l p c a		sup v v		inf v v		l p c a		sup v v		inf v v	
	a	b	c	d	c	d	a	b	c	d	c	d
1	5	15	15	11	10	8	2	10	13	12	10	9
2	12	11	13	10	12	8	1	8	14	12	10	7
3	8	12	14	10	11	8	2	10	14	12	10	8
4	11	12	10	12	11	8	3	7	12	13	9	9
5	7	12	13	12	11	9	2	8	14	11	10	9
6	10	10	13	12	10	8	2	6	12	13	9	9
7	12	10	14	13	10	8	2	7	13	13	10	9
8	13	10	13	12	11	6	3	6	14	13	10	7
9	8	12	15	12	11	8	2	8	14	12	9	8
10	10	10	13	10	11	9	2	7	13	12	10	7
Mean	10	11	13	11	11	8	2	8	13	12	10	8

ed by the long posterior ciliary nerve the short posterior ciliary arteries and nerves and a few veins The long posterior ciliary artery has a structure typical of an artery The endothelial cells are innermost with internal elastic lamina and a thick muscularis on the outer side surrounded by adventitia

In a horizontal cross section of the pig eye (Fig 1) the long posterior ciliary artery is seen to run along the outer surface of the sclera and to pierce the sclera in a shallow curve in the anterior part of the eye After passing through the sclera at the ora serrata the long posterior ciliary artery continues its course into the iris along a groove in the internal surface of the sclera accompanied by the long posterior ciliary nerve With higher magnification the endothelial cells internal elastic lamina and thick muscularis can be distinguished in this artery The long posterior ciliary nerve running alongside it has the typical structure of a nerve (Fig 2)

The equatorial cross section of the pig eye shows the long posterior ciliary artery and nerve on the external surface of the sclera They are surrounded by profusely pigmented connective tissue which is of slighter amount than the thick bundles of collagenous fibres of the sclera (Fig 3)

The long posterior ciliary artery is divided into two branches each passing into the iris where they form the major arterial circle of the iris (Fig 4)

The vortex vein has a wide lumen and a thin wall The wall consists of endothelial cells the internal elastic lamina and perivascular adventitia

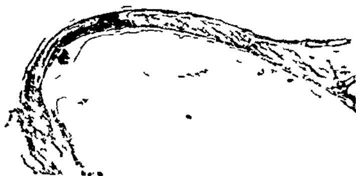


Fig 1
Horizontal cross section of pig eye The long posterior ciliary artery and nerve run along the external surface of the sclera to the anterior part of the eye.
PAS hematoxylin, × 7

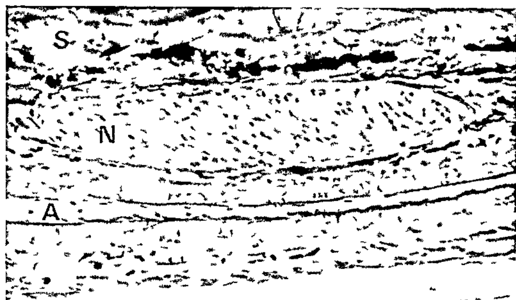


Fig 2
The long posterior ciliary artery (A) and nerve (N) on the surface of the sclera (S)
PAS hematoxylin × 250

B The injection digest bleaching method for studying the minute vasculature of the pig iris

Ink proved to be too weak a contrast medium After trypsin digestion bleaching and PAS hematoxylin staining ink injected into the long posterior ciliary artery failed to show the arteries appreciably better than without such injection

Indian ink injected into the long posterior ciliary artery followed by trypsin digestion bleaching and PAS hematoxylin staining improved visualisation of the major arterial circle of the iris and of the arteries running from it to the ciliary body and the iris Besides the arteries the myelinated nerves were beautifully visualised they stained dark purple and could be observed up to the long posterior ciliary nerve (Fig 5)

Indian ink injected into the vortex vein followed by digestion bleaching and PAS hematoxylin staining made the veins of the iris clearly visible Capillaries could also be seen (Fig 6) In many preparations however Indian ink did not make the vessels of the iris sufficiently visible

Injection of 5 per cent aqueous solution of Soluble Berlin blue into the vortex vein followed by trypsin digestion bleaching and PAS hematoxylin staining caused the veins to become clearly visible The capillaries were also visible up to the pupillary margin (Fig 7) The eye of which the long posterior ciliary artery had been injected with 5 per cent aqueous solution of Soluble Berlin blue showed contrast medium in the lumen of this artery in paraffin sections In a



Fig 3

Equatorial cross section Pigment containing connective tissue surrounds the long posterior ciliary artery (A) and nerve (N) Hematoxylin eosin × 250



Fig 4

Bifurcation of the long posterior ciliary artery (A) The long posterior ciliary nerve (N) accompanies the artery Weigert van Gieson × 80

flat preparation of the iris of the same eye digested bleached and stained with FAS hematoxylin the arteries were visible with the contrast medium

Neoprene latex injected into the long posterior ciliary artery followed by

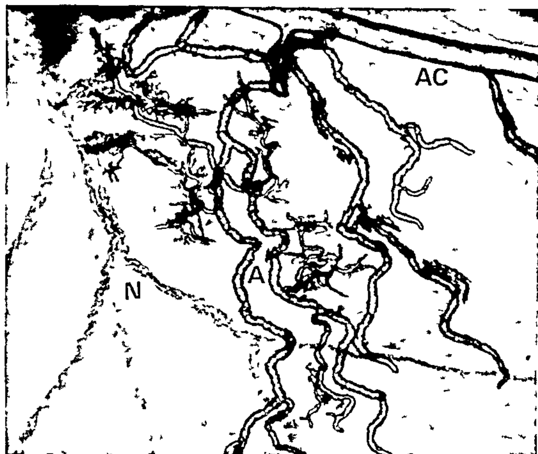


Fig 8

Indian ink injected into the long posterior ciliary artery The iris has been digested bleached and stained with PAS hematoxylin The major arterial circle of the iris (AC) radial arteries (A) and myelinated nerves (N) are visible × 80

digestion bleaching and PAS hematoxylin staining made the arteries of the iris clearly visible Besides arteries the myelinated nerves stained dark purple and were well visualised (Fig 8) Neoprene latex injected into the vortex vein caused the iris veins to become visible Besides veins the myelinated nerves were beautifully visible (Fig 9) Injection of Neoprene latex coloured red into the long posterior ciliary artery and of Neoprene latex coloured blue into the vortex vein followed by trypsin digestion bleaching and PAS hematoxylin staining made the veins and arteries of the iris simultaneously visible A separate plexus of myelinated nerves which stained dark purple with PAS hematoxylin was also seen

The long posterior ciliary artery divided into two branches either on the external surface of the sclera during the passage through the sclera or just before entering the iris The branches of the long posterior ciliary artery passed



Fig 6

Indian ink injected into the vortex vein The iris has been digested bleached and stained with PAS hematoxylin The veins of the iris are visible × 90



Fig 7

5 per cent aqueous solution of Soluble Berlin blue has been injected into the vortex vein The iris has been digested bleached and stained with PAS hematoxylin Capillaries are visible at the pupillary margin × 133



Fig 8
Injection (Neoprene latex) digest bleaching flat preparation of the pig iris Radial *arteries (A) and myelinated nerves (N) are visible PAS hematoxylin × 80*

on into the iris forming the major arterial circle of the iris in its ciliary part Radial arteries branched off from the major arterial circle of the iris into the ciliary body and the iris

The iris veins passed radially into the ciliary body and joined the vessels running from there to the vortex vein The anterior choroid showed a profuse network of anastomoses between the branches of the neighbouring vortex veins

The long posterior ciliary nerve sent out a rich plexus of myelinated nerves to each side of the ciliary body Smaller branches of these passed into the choroid A strongly developed nervous plexus ran towards the ciliary part of the iris and to the root of the iris (Fig 10)



Fig 9

Neoprene latex injected into the vortex vein The iris has been digested bleached and stained with PAS hematoxylin The veins (V) and myelinated nerves (N) are visible × 30

Discussion

Zietzschmann (1906) and Barth (1927) regarded as principal veins (venae vorticosae) the pig eye vessels running nasally in horizontal meridian and temporally but slightly lower down In the present work histological examination showed that these vessels were arteries Prince Diesem Eglitis and Ruskell (1960) considered these vessels to be arteries but reported that within the sclera they assumed a position closer to the surface which is adjacent to the choroid In the present work the long posterior ciliary artery was found to reach the ocular surface 10 mm nasally and 2 mm temporally to the optic nerve to pass along the external surface of the sclera and to pierce the sclera 11 mm nasally and 8 mm temporally to the limbus Barth (1927) though supposing these vessels to be veins observed that they ran along the external surface of the sclera to the conjunctival fornix where they pierced the sclera In the pig the branches of the long posterior ciliary artery form the major arterial circle in the ciliary part of the iris

From the pig iris the veins run radially to the ciliary body joining the ves



Fig 8

Injection (Neoprene latex) digest bleaching flat preparation of the pig iris Radial arteries (A) and myelinated nerves (N) are visible PAS hematoxylin × 80

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From the Ophthalmic Department Centralsygehuset DK 4700 Næstved Denmark (Head V Clemmesen M D) and the Health Service of Umanaq Greenland (Medical officer P H Alsbirk)

PRIMARY ANGLE CLOSURE GLAUCOMA (a c g) IN GREENLAND

BY

VIGGO CLEMMESEN and P H ALSBIRK

Introduction

Greenland is the largest island in the world with an area of about 826 000 sq miles To day Greenland has about 4? 000 inhabitants born in Greenland as well as about 6000 of Danish origin The Greenlanders are Eskimos to some extent interbred with Europeans but the prevailing type remains Eskimoan Ninety per cent of the Greenlanders live along the west coast the remaining ten per cent at the east coast The latter have been nearly without genetic connexion with the population of the west coast for several centuries Sixty four per cent of the Greenlanders live in seventeen small towns while the rest are scattered in small villages and settlements

There are no ophthalmologists permanently in Greenland Only during the summer a small number of Danish ophthalmologists attend the population of the coast The work is overwhelming strenuous and rather difficult as it is not possible to embark on a rocky coast or in a primitive harbour or to travel by dog team with the ordinary heavy instruments of a stationary clinic In the towns the ophthalmologist works at the hospital in the villages in a classroom in the school

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four hours in 0 25 per cent potassium permanganate solution and washed in water kept for six min in 5 per cent oxalic acid solution and washed in distilled water The flat preparation was floated on a slide dried and stained with PAS hematoxylin

The capillaries of the pig iris were most clearly brought out with 5 per cent aqueous solution of Soluble Berlin blue Indian ink filled the arteries veins and capillaries uniformly but often failed to make the vasculature of pig iris sufficiently clearly visible 5 per cent aqueous solution of Soluble Berlin blue made the veins and capillaries of the pig iris clearly visible whereas the arteries were not so beautifully visualised Neoprene latex made the arteries and veins of the pig iris clearly visible the capillaries did not fill so well as with Berlin blue

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in Copenhagen where some of the patients had been operated Table 1 shows the results (Clemmesen & Alsbirk 1969) There are more than twice as many cases of a c g in women than in men Of the women above the age of forty 2 1 per cent suffer from a c g and in the seventh decade of life the percentage rises to 3 7 a quite unusually high prevalence of the disease

The Initial Prevailing Symptoms of A. C G

It may be interesting to consider the symptoms which caused the patients to con sult the doctor Table 2 shows the result The dominating initial symptoms are genuine glaucoma attacks and headache The patients who showed visual loss as the first symptom suffered mostly from the so called creeping a c g (Lowe 1966) One man had seen haloes around lights as the only symptom Generally this symptom was not significant for the diagnosis of a c g in Greenland The Greenlanders are very courteous people If they imagine that the doctor is in terested in their seeing haloes they will admit it willingly

Preventive Screening Measures and their Results

The high prevalence of such a serious eye disease among a scattered population

Table 1

Primary glaucoma in Greenland in 1963 (Clemmesen & Alsbirk 1969)

n Number of patients % percentage of glaucoma

Age	Angle closure glaucoma				Open angle glaucoma			
	men		women		men		women	
	n	%	n	%	n	%	n	%
below 40	1		3		0		0	
40–49	3	0 19	7	0 54	0		0	
50–59	9	0 48	[illegible]	2 6	2		3	
60–69	8	0 69 } 0 9	[illegible]	3 7 } 2 1	2	0 2	4	0.5
70–79	5	1 28		3 0	1		0	
above 80	0		0		1		0	
number of persons	26		68		6		9	
total	94				15			

Previous Reports about Glaucoma in Greenland

The first who mentioned glaucoma as a very common cause of blindness in Greenland was Norman Hansen in 1911 He worked as medical officer in Greenland but specialized later in ophthalmology The next ophthalmologist who went to Greenland was V Hertz (1926 1928 1932 and 1938) He was also impresssed by the serious cases of glaucoma he saw and in 1926 he succeeded in ensuring that all the hospitals in Greenland were supplied with pilocarpine

After the last war Lawætz made a three months journey in 1948 along most of the west coast examined 1500 patients (of a population of about 15 000) and found twenty nine patients suffering from primary or secondary glaucoma Here it must be remembered that in those years there were only 900 persons above sixty years of age in the whole of Greenland (about 650 amongst the population examined) It must also be considered that until the last few years the diagnostic conditions have not been favorable for detection of glaucoma The medical officer were then as now without ophthalmological training and until 1960 the hospitals were not all provided with tonometers So the diagnosis of glaucoma was not at all easy The ophthalmologists had similar difficulties An ophthalmoscopy does not reveal a c g as the optic disc remains normal for rather a long time of the course of the disease The equipment did not include a slit lamp or even a slit loupe Finally the person interpreting often has a very superficial training so that the anamnesis is often imperfect Consequently it would often be rather difficult to discern between primary and secondary a c g Many patients who have had angle closure attacks but who have received insufficient treatment show posterior synechias

Here a typical case history may be mentioned In 1959 a woman from a small village in the far north came to consult the ophthalmologist who worked in the district town She complained of headache ophthalmoscopy showed normal optic discs and she was given a prescription for glasses that she certainly needed Five years later (1964) she was examined again Her optic discs now showed severe cupping and the vision of both eyes was very poor A more thorough questioning revealed that the woman had suffered from repeated angle closure attacks during the last fourteen years When se was examined again in 1969 she had become totally blind and her daughter had dangerously narrow chamber angles but had not as yet subjective symptoms

The Present State of Primary Glaucoma in Greenland (1968)

It is not easy to get a general view of so special a disease in such a vast country with a scattered population In 1968 it became possible to visit fifteen of the seventeen medical districts of Greenland (Clemmesen) and to perform gonioscopy on ninety four per cent of the already known cases of primary glaucoma The task was difficult as all other sorts of ophthalmic work including refraction had to be done and the time was limited Supplementary information was requested from the two remaining districts and from the University Eye Clinic

glaucoma the screening revealed eleven new cases six of them a c g in women After the screening each individual case was subjected to an ophthalmological examination including ophthalmoscopy applanation tonometry (Draeger s instrument) and above all minute gonioscopy by means of a Koeppe lens and a hand held microscope (Haag Streit) Of the six women suffering from a c g four had creeping a c g two had an accidental pressure rise at the time of the screening

One case which was not detected by the screening may be mentioned A man had normal intraocular pressure at the screening and no subjective symptoms at all but the anterior chambers looked very shallow seen by the naked eye At later examinations the tension remained normal As later on his daughter was found to suffer from a c g he was subjected to a dark room test and the pressure rose to 66 and 42 mmHg respectively

2. Gonioscopic screenings

Since the intraocular pressure is generally normal between attacks detection of a c g by tonometric screenings is generally not to be expected To discover such cases systematic gonioscopy must be the most suitable tool Consequently a gonioscopic screening of the normal tension group from the tonometric screening was performed the examination consisting in ophthalmoscopy and applanation tonometry followed by direct gonioscopy In this way 52 men and 52 women or 75 and 88 per cent respectively of the population over forty years of age in the town were examined This gonioscopic screening revealed dangerously narrow angles in one man and in ten women By provocation test two new cases of a c g were detected among them (Table 3) Stimulated by this success similar gonioscopic screenings were performed in other parts of Greenland Two of these should be mentioned The first at *Scoresbysund on the east coast* was of special interest because the population here is purely Eskimoan This screening comprised all the persons over forty twenty four men and thirty women Amongst these fifty four persons one man and four women with dangerously narrow angles were found By the following provocation test (*Kirsch s triple test*) one woman showed a pressure rise from 17 to 46 mmHg On the others the test gave a negative result as regards tension but the angle closed nearly completely and in the case of one person there were anamnestic complaints of headache accompanied by rainbow vision probably a case of intermittent a c g but the diagnosis could not be verified

The second screening to be mentioned was in a small rather isolated village named *Kraulshavn in the northern part of the west coast* Beside ordinary ophthalmological work a gonioscopic screening was performed on thirteen of the seventeen persons over forty The result was rather depressing (Table 4) As the doctors boat had broken down it was unfortunately not possible to bring

Table 2
The initial subjective symptoms in previous known cases of a c g

	Attacks	headache	visual loss	haloes	total
Males	7	11	4	1	24
Females	33	20	4	0	55

on an arctic island mostly without ophthalmological care makes preventive measures desirable for the detection of early cases instruction of the medical officers as well as education of the population

1 Tonometric screening

The first systematic attempt to detect new cases of glaucoma in Greenland was a tonometric and anamnestic screening performed by the medical officer of Umanaq district P H Alsbirk (in 1967) The occasion was a remarkable series of dramatic glaucoma attacks among the population The screening comprised all persons who were over forty years of age Altogether 396 persons or 99 per cent were examined (Table 3) Apart from the eleven previous known cases of

Table 3
Primary glaucoma in the medical district of Umanaq (Clemmesen & Alsbirk 1969)
2289 inhabitants 399 over 40 years of age 396 examined

Sex	known before screening		detected by tonometric screening		detected by gonioscopic screening		total	
	M	F	M	F	M	F	M	F
Angle closure glaucoma	0	10	0	6	0	4*)	0	20
Open angle glaucoma	0	1	2	2	0	0	2	3
Combined type glaucoma	0	0	0	1	0	0	0	1
Total	0	11	2	9	0	4	2	24

*) Two of the cases were found by screening of the elderly persons who come to consult the oculist

great importance to know the depth of the anterior chamber Consequently despite all the technical and climatic difficulties the anterior chamber depth was measured in 843 pairs of eyes in the district of Umanaq (Alsbirk) (That is ninety five per cent of the population above seven years of age in the town and above forty in the villages) The measurements were performed by means of the Haag Streit 900 slitlamp device The graph in fig 1 shows the results To facilitate comparison the chamber depth in Europeans measured by Tornquist Sweden on 398 normal right eyes is also marked The maximum in chamber depth at the age of fifteen is an interesting observation which apparently has not been made in earlier studies of this subject It is evident that Greenlanders have a much lower chamber depth than Europeans The chamber depth in the Danes at Umanaq corresponded perfectly to the Swedish measurements In the figure some gonioscopic findings from the screenings (from 136 persons) are also plotted In women the angles are much narrower than in men Correspondingly table 6 shows that only three per cent of the men but twenty nine per cent of the women have narrow angles a difference which is significant ($\chi^2 = 16.2$ $P < 0.001$)

The correlation between the assessment of the gonioscopic findings and the quite independent measurement of the chamber depth (performed by Alsbirk) is given in table 7 It is shown that there is a fairly good agreement between these two anatomical factors in the etiology of a c g

Summarizing the results it appears that both gonioscopy and the measurement

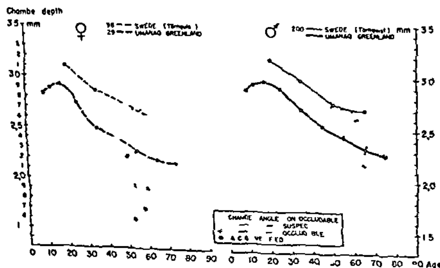


Fig 1
The correlation between the gonioscopic findings and chamber depth

Table 4

Results of a gonioscopic screening in the village of Kraulshavn, comprising 13 of the 17 persons above 40 years of age

1) a woman 66 totally blind from a c g
2) her daughter 46 angles occludable
3) a woman 57 with nearly closed angles
4) a man 50 with occludable angles

all these persons to the town in the small motor boat with which it was replaced It was only possible to take two of the persons in the boat One of these was the woman no 3 who next day responded to a provocation test with a pressure rise to fifty one mmHg The other person was a woman from another village who had lost the vision on one eye from an attack the year before and who had nearly completely closed angles She had no understanding of the benefit of pilocarpine drops Both patients were subjected to iridectomy the next day This report gives a fair illustration of ophthalmological working conditions in the isolated places of Greenland

Table 5 shows the total result of all the goniocopic screenings performed (Clemmesen & Alsbirk 1970) The table demonstrates that gonioscopic screening is a suitable measure in the detection of a. c g

3 The anterior chamber depth in Greenlanders

In the assessment of the probability of angle closure in a given person it is of

Table 5

The results of gonioscopic screenings (236 persons above 40 years) (Clemmesen & Alsbirk 1970)

Chamber angle	Males	%	Females	%	Total	%
total	99	100	137	100	236	100
non occludable	93	94	102	75	195	83
suspect	4	4	6	4	10	4
occcludable	2	2	29	21	31	13
Provocation test						
positive	1	1	9	6	10	4
negative	2		7		9	

Table 8

PTC taste testing a m Harris & Kalmus

nt % percentage of nontasters			n total number of examined			
Becker & Morton (1964)	normal		a c g		o a g	
	nt %	n	nt %	n	nt %	n
Caucasians	28 %	446	17 %	155	53 %	211
Negroes	17 %	14[illegible]	0	30	37 %	80
Alsbirk & Alsbirk						
Greenlanders	57 %	313	54 %	50*)		
Danes	34 %	6				

*) a c g patients (1[illegible]) plus siblings and children to a c g patients (38)

other hand open angle glaucoma patients were less sensitive than normal persons

As this test had not yet been tried in Greenland it was applied to 363 Greenlanders and 76 Danes (Alsbirk) When the 313 normal Greenlanders were divided in two groups according to their chamber depth above or below the mean, the result was fifty six and fifty seven respectively It may be concluded as a preliminary result that nontasters are much more frequent among Greenlanders than among most other populations The sensitivity to PTC has no relation to the chamber depth here

Instruction of the medical officers and of the population

Among the preventive measures instruction of the *medical officers* and of the population must play a very important part The ophthalmological knowledge of Danish physicians is not sufficient to meet the glaucoma situation in Greenland Consequently a *compendium* has been written on eye diseases in Greenland and their proper treatment (Clemmesen) The meetings of the medical officers every second year are also used for renewed consideration of the problems concerning glaucoma and quite often telegraphical questions have to be answered All *hospitals in Greenland* are now provided with Schiotz tonometers slit loupes and all sorts of medicine for the treatment of glaucoma At the same time it must be emphasized that it is necesssary to instruct the population about glaucoma above all attention must be drawn to the prodromals such as headache blurred vision and haloes around lights The patients ought to consult the doctor during an attack so that tonometry can solve the question of

whether the symptoms are due to an intraocular pressure rise or not. A broadcast of a short appeal of this kind gave us three more cases in one medical district. In one of these persons rainbow-vision had been the only symptom. A printed folder about glaucoma in Greenlandic to be given to patients and their relatives is being prepared

At the moment there are relatively few elderly people in Greenland (Fig 2) but in the coming years their number will increase according to the calculations made by the Ministry for Greenland (Table 9) It is probable that the number of glaucoma cases will increase correspondingly and make preventive measures more and more necessary

Comments

To explain the extraordinary prevalence of a c. g in Greenland it is most natural to assume that several of the original relatively few Eskimoan immigrants who came from Canada to Greenland several centuries ago brought with them a predisposing factor so called genetic drift a certain amount of inbreeding has followed and has aggravated the situation

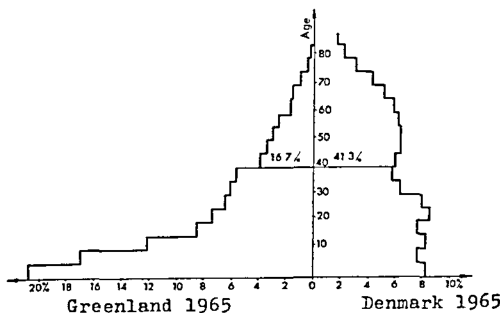


Fig 2

Percentage distribution of the population of Greenland and Denmark (Clemmesen & Alsbirk 1969)

Table 9
The probable increment of the population of Greenland

Group of age	1970–1980	1970–1990
Above 40 years	35 per cent	71 per cent
Above 50 years	3. per cent	81 per cent
Above 60 years	49 per cent	86 per cent

It is natural to ask for information about the prevalence of a c g *among* the Eskimos in Canada and Alaska As far as we have been able to learn only sporadic cases have been *reported* Thus *Milo Fritz* (1968) in Alaska and Elizabeth Cass in North West Canada (1969) have only seen a few cases of a c g and no cases of open angle glaucoma The only colleague who has reported a higher prevalence of a c g in Canadian Eskimos is John S Speakman (1968) Among 900 adult Eskimos in Baffin Island and on the north coast of Quebec he found three cases of a c g and two with advanced chronic glaucoma It is probably not realistic to assume that the scattered Eskimoan race is a genetic unity but it is natural to suppose that the Eskimos in the most easterly part of Canada (e g Baffin Island) belong to the same branch of the Eskimos as the Greeenlanders Consequently it would be of immense interest to perform *systematic gonioscopic* screenings in Eskimo communities in the eastern part of Canada and to *measure* anterior chambers depths there

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whether the symptoms are due to an intraocular pressure rise or not A broad cast of a short appeal of this kind gave us three more cases in one medical district In one of these persons rainbow vision had been the only symptom A printed folder about glaucoma in Greenlandic to be given to patients and their relatives is being prepared

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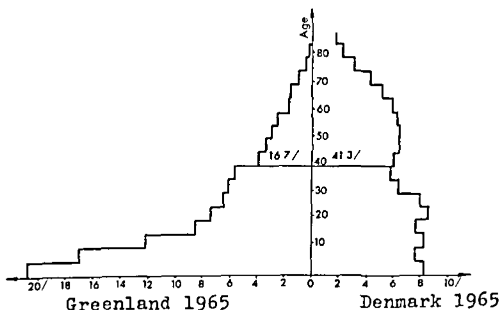


Fig 2
Percentage distribution of the population of Greenland and Denmark
(Clemmesen & Alsbirk 1969)

From the Ophthalmic Department Centralsygehuset DK 4700 Næstved Denmark (Head Viggo Clemmesen M D)

PROBLEMS IN GONIOSCOPIC SCREENINGS IN GREENLAND

Technique classification of findings diagnosis

BY

VIGGO CLEMMESEN

Choice of method and technique

Because of the unusual working conditions for the ophthalmologist in Greenland in hospital wards classrooms or other available rooms he must bring all his instruments with him by air by sea or by dog team and cannot use traditional equipment Consequently both the instrumentation and the examination methods must be adapted to these conditions

Typical gonioscopic screening consists of ophthalmoscopy followed by tonometry by means of the hand held Draeger applanation tonometer and finally direct gonioscopy Thus the whole examination can be performed with the patient in supine position generally on a school table with a blanket as a cushion under the back of the head The examination generally takes about seven to eight minutes The next patients are waiting in the room and so do not need much explanation about the examination

Direct gonioscopy by means of the Koeppe lens is little used in most countries although it is simple in use and is strongly advocated by an experienced gonioscopy such as Robert Shaffer (1962) Most ophthalmologists prefer indirect gonioscopy by means of the Goldmann prism or similar lenses but this method

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able angles lies about an angle of twenty degrees but some of the so called twenty degree angles are of claw form and can be occluded when the pupil dilates other twenty degree angles with a plane not convex iris diaphragm are not capable of closure In accordance with this point of view Bernhard Becker (1967) concludes that the angle classification must be based upon the shape of the angle and its capacity for closure not on which of the details that are visible

Generally the brown iris diaphragm of old women of Eskimoan type is con vex giving a more or less typical shadow by side light as illustrated by Becker & Shaffer (1965) and correspondingly the lens looks rather thick viewed through the biomicroscope

Since the aim of a gonioscopic screening is to detect latent cases of angle closure glaucoma (a c g) the greatest importance should be attached to the judgment of whether or not the angle is occludable For this purpose we use the usual classification by Becker & Shaffer (1965) but differentiated a little in the middle of the spectre (Table 1)

A standard gonioscopic examination should consist of three parts First the angle is scrutinized all the way round Next the narrowness of the angle is re corded in the four main meridians in a diagram for each eye Finally the ca pacity for closure of the angle as a whole must be assessed and noted In this evaluation for which clinical experience is required the shape of the angle must as mentioned before be considered as a most important factor

Table 1
(Viggo Clemmesen)

Angle occludable	0 Closed angle 1 Slit like angle just a small rim of the antetrabecular meshwork is visible (Grade 1 Becker & Shaffer 1965) *Angle closure probable* eventually 2 Very narrow angle (Grade 2 Becker & Shaffer) *Angle closure possible* 3 Narrow angle of claw form. About one half of the trabecular mehwork is visible *Angle closure possible*
Angle nonoccludable	4 Narrow angle (Grade 3 Becker & Shaffer) About one half of the trabecular meshwork is visible, *but the angle is considered nonoccludable* Open angle (Grade 4 Becker & Shaffer) Angle closure is *impossible*

has several disadvantages The indirect lenses tend to exaggerate the narrow ness of an angle and considerable skill is required to maintain binocularity when looking into the horizontal angles (Pollack 1967) Pressure on the centre of the cornea can with some models temporarily open a closed angle (Shaffer 1967) S C Becker (1969) states that the appearance and resulting grading of any given angle varies with the prism used For gonioscopy in Greenland it is the most important disadvantage of the indirect method that a stationary biomicro scope is only rarely at hand The direct procedure on the other hand is a more flexible method It can be used in any village or settlement using a hand held goniomicroscope (Haag Streit) provided with illumination supplied from a dry battery and the patient lying on a table or even on the sleeping platform of a hut

It is most important that if possible the chamber angle is examined all the way round because of the great variation in the narrowness of the angle in the different directions but this fact is not sufficiently emphasized in the litera ture It is strongly advisable to record the findings at once in a diagram for each eye (Fig 1) More superficial gonioscopy may lead to misconception of the nature of the case in question In too many case records the angle is only de scribed vaguely as "narrow" or open"

Clinical interpretation of gonioscopic findings

Becker & Shaffer (1965) state that the limit between occludable and non occlud

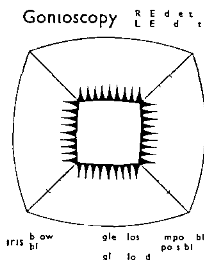


Fig 1

Diagram of recording angle width in different quadrants The dashed lines indicate the position of Schlemm s canal

Table 2
(Vi_ogo Clemmesen)

Classification of primary glaucomas (except congenital forms)

Occludable chamber angles

Potential an le closure glaucoma Persons with gonioscopically occludable chamber angles but at present without tonometric or gonioscopic proof of intraocular pressure elevation or closure of the angle Some have subjective symptoms such as headache accompanied by haloes and blurred vision others have not The diagnosis a c g has not been verified

Angle-closure glaucoma (a c g)

Latent a c g Patients with occludable chamber angles without subjective symptoms but with positive gonioscopic and tonometric response to provocation tests

Intermittent (prodromal a c g Patients with occludable angles and intermittent ob served pressure elevations accompanied by prodromal symptoms headache haloes and blurred vision, but with normal tension in the interparoxysmal periods

Acute a c g Patients with severe attacks of an_ole closure accompanied by pain and the other usual symptoms

Chronic a c g Patients with partially occluded chamber angles and constant intra ocular pressure elevation Some of the patients have no subjective symptoms (creeping a c g Lowe) others complain of he dache

Combined mechanism glaucoma (c m g)

Open angle glaucoma complicated by angle closure attacks due to anatomically narrow angles (Becker & Shaffer 1965)

Non-occludable chamber angles

Intraocular hypertension Persons with repeated tonometric values above 21 mmHg but without pathognomonic objective signs of open angle glaucoma Some may have suspect cupping of the optic d scs but without established evidence of glaucoma

Open angle glaucoma (o a g)

Latent o a g Patients with moderate intraocular pressure elevation where a clearly positive response to the water drinking test is the basis of the *diagnosis*

Chronic o a g Patients w th non occludable *chamber* angles intraocular tens on ele vation and s gnificant combinations of cupp ng of the optic discs field loss and signi f cantly positive water drinking test

the triple test gives angle closure and a pressure rise from 17 to 52 mmHg and she must be described as a latent a c g

This classification has been so satisfactory that it is now used in the daily work at our hospital in Denmark

In papers about provocation tests in cases of supposed angle closure glaucoma the closure of the angle is often mentioned as a more absolute condition than it really is If an angle closes totally upwards and to the sides and only a very narrow slit is visible below a closure must be said to be imminent but the angle should not be described as "closed" The outflow through this tiny slit may in itself be able to prevent the intraocular pressure from rising above the signifi cant level although the eye must be said to be in great danger of an acute attack of angle closure It is probable that the failure of the provocation tests in about fifty per cent of cases with previous angle closure attacks is to be explained in this way The actual trigger mechanism which release an acute attack is still unknown but it is probable that a congestion of the iris root plays a part

Classification of primary angle closure glaucomas

The investigations concerning a c g in Greenland have shown that the usual classification of a c g in four groups intermitttent acute chronic and plateau iris a c g (Becker & Shaffer 1965) is too summary not differentiated enough for scientific and practical purposes All ophthalmologists know the present discussion about intraocular hypertension and incipient open angle glaucoma In these cases there is time enough even years to find the right diagnosis On the contrary it is the cases of incipient or dubious a c g that are the more serious menace to health It may be admitted that in countries with easy access to ophthalmologists this question is not of great importance In Greenland how ever where access even to the medical officers is often difficult for many weeks of the year because of the distances and the difficulties of sea transport brought about by the changing arctic climate an acute attack of a c g is a very serious situation to encounter

The provocation tests are not very reliable and under the conditions prevail ing in Greenland it is not even possible to submit all persons with narrow angles to provocation tests Also the anamnestic information is not very reliable It has consequently proved to be convenient to use a more differentiated classifi cation (Table 2) The advantages can best be shown by examples

A 57 year old woman has occludable angles a chamber depth of 1 27 and 1 29 mm respectively but not as yet any subjective symptoms She refuses to come for a provocation test She should be classified as potential a c g and kept closely supervised Another woman has a history of prodromals such as headache and rainbow vision and has similar angles but a provocation test (the "triple test of Kirsch) does not give a significant pressure elevation 6 mmHg only Until she suffers a real attack or a new provocation test gives a positive response she should also be described as potential A third woman with occludable angles normotensive has absolutely no subjective symptoms but

The Department of Ophthalmology (Head Prof Viggo A Jensen)
Kommunehospitalet University of Århus DK 8000 Denmark

ON THE OPTICAL MEASUREMENT OF CORNEAL THICKNESS

BY

NIELS EHLERS and FINN KRUSE HANSEN

According to ancient literature the thickness of the central cornea is about one millimeter This value originates from post mortem anatomical measurements and corresponds fairly well to the thickness of the maximal swollen human cornea (*Ehlers* 1966)

Blix (1880) was the first to perform a direct optical measurement of the corneal thickness in a living eye From measurements on ten eyes he concluded that the central thickness of the cornea is about 0 5 mm in young men in good accordance with most later authors In recent years the study of the corneal thickness has been taken up and more simple instruments have been deviced (*von Bahr* 1948 *Maurice & Giardini* 1951 *Jaeger* 1952)

The purpose of the present paper is to review the different optical principles for the measurement of the corneal thickness and to discuss the use and the errors of the Haag Streit pachometer which will be used in some following clinical studies

I Optical principles

1 Successive focusing on specular reflexes
2 Simultaneous observation of specular reflexes
3 The use of an astigmatic light bundle
4 Simultaneous observation of doubled specular reflexes
5 Measurement of the apparent thickness of the optical section

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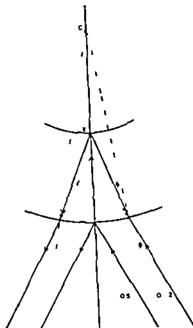


Fig 1
Successive focusing on specular reflexes (*Blix Ulbrich Hartinger*) With the apparatus in position 1 the light reflected from the anterior corneal surface in A is seen in the other microscope When the apparatus is moved to position 2 the light falls on B is refracted to E and reflected symmetrically back into the other microscope AD = d is the apparent thickness AE = x is the real thickness C is the center of curvature of the anterior corneal surface. The various angles used for the calculations are seen from the figure
In the figs the angles and the distances are not drawn to scale

$$x = r - \frac{(r - d) \sin \lambda}{n \sin (\alpha + \psi)} \qquad (1)$$

In this formula only $\sin (\alpha+\psi)$ is unknown and by rather long calculations a complicated expression of this as a function of λ r d and n may now be obtained *Blix* gave a table from which the thickness could conveniently be read directly It appears from this table that variation in the corneal radius within the normal range is of only minor importance for the result

As regards the accuracy of the method *Blix* says to use a mean value is not necessary since it will soon be recognized that the measurements fall in two groups the correct ones and the incorrect ones Therefore the accuracy is fully acceptable and the greatest error should not exceed 0 02 mm

Blix studied 10 eyes from 8 young men The values were in the range 0 482–

II The Haag Streit pachometer

1 The apparatus and its use
2 The significance of the angle kappa
3 Measuring accuracy

I Optical principles

1 Successive focusing on specular reflexes

By successive focusing on the anterior and the posterior surface of the cornea the distance moved by the apparatus is the apparent thickness From this the real thickness of the cornea can be calculated when the radius of curvature of the anterior surface and the refractive index of the cornea are known

Blix (1880) used two microscope tubes with optical systems of equal power converging at an angle of 39° towards a point in front of the tubes The apparatus was movable along the line bisecting the angle between the tubes An illuminated cross in the one tube gave an image at the point of intersection of the microscope axes The apparatus was at first so adjusted that this image by reflection in the anterior corneal surface was observed in the other microscope By moving the apparatus forwards along the line bisecting the angle between the two microscopes until the image was seen by reflection in the posterior surface the moved distance is the apparent thickness of the cornea From this the real thickness may be calculated exactly

Fig 1 shows the principle of the method With the apparatus in position 1 the light reflected from the anterior corneal surface in A is seen in the other microscope In position 2 the light falls on B is refracted to E and reflected symmetrically back into the other microscope The various angles are seen from the figure AD = d is the apparent thickness AE = x is the real thickness

To perform the calculation we know besides the apparent thickness d the radius of the anterior corneal surface r the refactive index n (*Blix* used 1 375) and the angle λ (= 19 5°) From $\triangle$ CBE the sine relations give

$$\frac{\sin(\tau-\alpha-\psi)}{r} = \frac{\sin\psi}{r-x}$$

from which

$$x = r - \frac{r\sin\psi}{\sin(\alpha+\psi)}$$

Inserting in this equation $\sin\psi = \frac{\sin\varphi}{n}$ and $\sin\varphi = \frac{(r\ d)\sin\lambda}{r}$ the latter obtained by the sine relations applied to $\triangle$ CBD we obtain

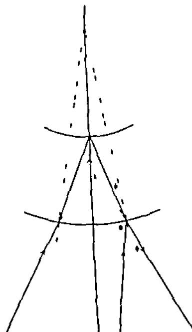


Fig 9

Simultaneous observation of specular reflexes (*Gullstrand Tscherning*) A strong light and a telescope are placed symmetrically around the perpendicular through the center of the cornea. The reflection from the posterior corneal surface is observed in the telescope A weak light is moved until its reflection in the anterior corneal surface is seen coinciding with the reflection from the posterior surface Indications as in fig 1

angle between the perpendicular to the center of the cornea and the incident ray from the weak light was measured When the anterior corneal curvature and the corneal refractive index were also known the real thickness of the cornea could be exactly determined by trigonometrical calculations similar to those of *Blix Gullstrand* in two eyes found 0 46 and 0 51 mm respectively *Tscherning* (1898 1904) also used this principle but another apparatus Apparently he measured only one person and found a thickness of 1 15 mm

3 The use of an astigmatic light bundle

Lindstedt (1916) developed a method for the measurement of the depth of the anterior chamber An astigmatic light bundle incident upon the cornea was adjusted with one focal line on the cornea and the other on the lens The adjustment of the two focal lines was made simultaneous The optical system was composed of a convex spherical lens and a cylindric lens The distance between the two lenses determined the distance between the two focal lines and the

0 668 mm and if one of his persons who showed both the upper and the lower extreme is excluded the range in 8 eyes is 0 506–0 576 mm

The so called *microscopic method of Donders* consists in successive focusing a microscope on the anterior and the posterior surface of the cornea Considering paraxial rays the real thickness may easily be calculated from the movement of the apparatus (fig 1) The microscope is in position 1 focused on the anterior surface of the cornea By moving to position 2 the posterior corneal surface is brought into focus The apparent thickness (= the displacement of the micro scope) *is d the real thickness x At the* anterior corneal surface *the difference* in vergence between the incident and the refracted rays equals the vergence power of the surface One may therefore write

$$\frac{1}{d} - \frac{n}{x} = \frac{n-1}{r}$$

from which by multiplication with rxd

$$x = \frac{ndr}{r + d\,(n-1)} \qquad \text{(Hartinger 1921)}$$

This method is simple in use The readings can be made with an accuracy of 0 1 mm (*Hartinger* 1921)

The greatest obstacle to the use of the method of successive focusing is the possibility of a movement of the cornea between the two adjustments which will of course invalidate the result

Schiotz (1913) used this principle for thickness measurements on excised cor neae With the cornea placed on a glass hemisphere the focusing on the posterior surface was facilitated and the possibility of a displacement of the cornea bet ween the two successive adjustments was avoided *Ulbrich* (1914) introduced the use of a slit lamp and a corneal microscope provided with a micrometer drum to measure the displacement of the microscope *Fincham* (quoted by *Koby* 1930) used this principle and in 12 eyes found values from 0 48 to 0 59 mm (mean 0 53 mm) and *Sobanski* (1934) also using this principle found a value of 0 407 to 0 671 mm for the central cornea

2 Simultaneous observation of specular reflexes

Gullstrand (1909) used the reflection of a weak light from the anterior and of a strong light from the posterior corneal surface The strong light and a tele scope were placed symmetrically 25° from the perpendicular through the cen ter of the cornea and adjusted so that the reflection from the posterior surface was seen in the telescope The perpendicular to both the anterior and the poste rior corneal surface was first determined by coinciding reflections The weak light was now moved until its reflection in the anterior surface was seen in line with the reflection of the strong light from the posterior surface (fig 2) The

the reflection from the anterior corneal surface is seen in the microscope If the axis of the apparatus (= the line bisecting the right angle between incident and reflected light) coincides with the perpendicular common to both corneal surfaces the glass plates may be turned and the reflection from the posterior corneal surface seen to coincide with that from the anterior surface

The displacement a of the light by passing a plane glass plate of thickness b is seen from fig 3 From △ FGH we may write

$$\sin(\delta - \varepsilon) = \frac{a}{FG} = \frac{a \cos \varepsilon}{b}$$

$$a = \frac{b \sin(\delta - \varepsilon)}{\cos \varepsilon} \qquad (2)$$

For the calculation of the real thickness of the cornea we may proceed as in the method of *Blix* Equation (1) is valid also in this case and by inserting $d = a/\sin \lambda$ the only unknown is $\sin(\alpha + \psi)$ which may again be expressed by a rather complicated formula *von Bahr* gives a graph showing angle of rotation of the glass plate versus corneal thickness for an average corneal radius of 7 8 mm By way of examples *von Bahr* has shown how variation in corneal curvature only insignificantly affects the calculated thickness of the cornea

The accuracy of this method was studied by double determinations on 36 eyes from 18 persons From this the standard deviation for a single reading was found to be 0 013 mm In a measurement of 224 eyes from 125 persons a mean value of 0 565 ± 0 002 mm (mean ± standard error of mean) was found

Maurice & Giardini (1951) designed an attachment to the Haag Streit slit lamp model 360 A glass plate was placed on the slit lamp arm between the slit and the focusing lens and covering the half of the light beam The arm of the slit lamp and the microscope were fixed at an angle of 50° The slit was focused on the cornea with the reflection from the anterior surface seen in the microscope The glass plate was now rotated until the reflection from the posterior surface was seen aligned with that from the anterior (fig 4) As a theoretical calculation of the real thickness has not been possible the apparatus was empirically calibrated on glass tubes of known wall thickness This apparatus which is commercially available (Sterks Martin London) has been used extensively in studies on corneal physiology The theoretical background of the apparatus has recently been treated by *Kalberer Walz & Grun* (1965) and *Walz Gautschi & Grun* (1968)

The scale of the apparatus can be read to 0 25 corresponding to a thickness of about 0 005 mm The accuracy of the method was estimated by taking 25 readings in one position on one eye resulting in a standard deviation of 0 011 mm *Maurice & Giardini* measured the corneae of 44 subjects and gave a value of 0 507 ± 0 0042 mm (mean ± standard error of mean N = 44)

chamber depth could be calculated *Rosengren* (1930) used this apparatus for studies on the chamber depth A commercially available modification has been described by *Stenstrom* (1953)

The principle although it seems accurate apparently has not been used in the study of corneal thickness

4 Simultaneous observation of doubled specular reflexes

von Bahr (1948) designed an apparatus in optical principle similar to that of *Blix* but permitting simultaneous observation of the anterior and the posterior corneal surface Plane parallel glass plates were placed in the lower half of the incident and the reflected light (fig 3) The glass plates were symmetrically movable around vertical axes With the glass plates perpendicular to the light no refraction takes place and in this position the apparatus is so adjusted that

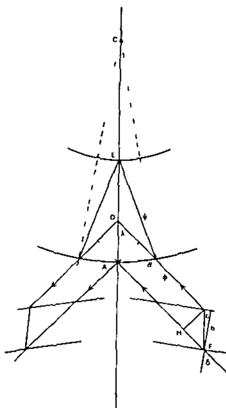


Fig 3

Simultaneous observation of doubled specular reflexes The principle of *von Bahr* Plane parallel glass plates in the lower half of the incident and the reflected light bring the reflection from the posterior corneal surface to coincide with that from the anterior The displacement of the light by the plane parallel glass plate is calculated from △ FGH Indications as in fig 1

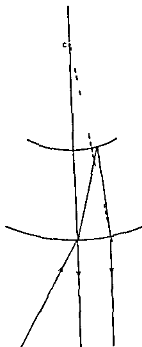


Fig 5
Measurement of the apparent thickness of the optical section The principle of *Juillerat & Koby Paycha Donaldson* The optical axis of the microscope coincides with that of the observed cornea and the apparent thickness of the optical section is measured Indications as in fig 1

axis of the microscope coincides with that of the eye The angle of incidence of the light upon the cornea may be 45 (*Koby* 1928) 71° (*Paycha* 1953) or 51 5° (*Donaldson* 1968) When the angle of incidence is around 71° the apparent thickness equals the real thickness as emphasized already by *Juillerat & Koby* (1928)

Koby (1928) measured 20 subjects and found a value of 0 590 ± 0 014 mm (mean ± standard error of mean) This high mean value is partly due to the assumption of a refractive index of 1 4 and the high standard error probably to the use of an eye piece micrometer requiring two successive readings to obtain the apparent thickness *Donaldson* (1968) measured 263 eyes and gave a value of 0 5?? ± 0 041 mm (mean ± standard deviation number of statistically independent values not given) As to the accuracy *Donaldson* gives an average deviation in consecutive readings of 1 2 % A part of this material was more thoroughly reported by *Martola & Baum* (1968)

Jaeger (195?) developed the principle illustrated in fig 6 The apparatus is available as an attachment to the Zeiss slit lamp (Zeiss Oberkochen) and a simi

Fig 4
Simultaneous observation of doubled specular reflexes The principle of *Maurice & Giardini* A plane parallel glass plate (not shown) is placed in the incident light in front of the focusing lens (K) When the glass plate is rotated the reflection from the posterior surface is aligned with that from the anterior surface Indications as in fig 1

Hedbys & Mishima (1962) designed a similar apparatus for experimental use The plane glass plate was placed in the reflected light behind a condensing lens The apparatus was calibrated against the apparatus of *Maurice & Giardini*

5 Measurement of the apparent thickness of the optical section

The principle of the following methods is a measurement of the apparent thickness of the optical section which is seen by diffuse reflection from the colloids of the cornea (the Tyndall phenomenon) Dependent upon the angle of incidence of the light and the observation angle the real thickness may be calculated in different ways from the measured apparent thickness (*Juillerat & Koby* 1928) The measurement of the apparent thickness is improved and simplified by simultaneous observation of the anterior and the posterior surface as introduced by *Goldmann* (1932)

The main optical principles of calculation were treated by *Juillerat & Koby* (1928) and two appeared particular simple (figs 5 & 6) In the first the optical

Haag Streit slit lamp the scale is linearly calibrated in mm thickness and correction for variations in r and in non linearity is made by a table *Hedbys & Mishima* (1968) using the Haag Streit apparatus found a value of 0 518 ± 0 003 mm in 40 eyes (mean ± standard error of mean number of subjects not stated) *Lowe* (1969) found 0 517 ± 0 003 mm (mean ± standard error of mean) in 157 eyes from 80 subjects

The same principle was used by *Lavergne & Kelecom* (1962) who found a value of 0 51 ± 0 003 mm (mean ± standard error of mean) in 198 eyes the only difference being an angle of incidence of 60° and the use of the *Goldmann* messokular (193?) The method is discussed by *Weekers Grieten & Lavergne* (1961)

Jaeger stated that the angle of rotation of the glass plate could be read with an accuracy of 0 5 corresponding to 0 02 mm in apparent thickness *Honegger & Genee* (1968) gave for a slightly modified attachment to the Zeiss slit lamp a 95 % probability of being within ± 0 01 mm of the real value when taking the mean of 5 readings By the attachment to the Haag Streit slit lamp the same accuracy was obtained by 4 readings

An objection to this principle is that the measurement is made along the line of sight and not along the optical axis *Mishima & Hedbys* (1968) proposed the use of two small additional lights the reflections of which made it possible to perform the measurement with the light falling perpendicular to the anterior corneal surface In this situation the patient had not to fix the incident light but another movable mark.

II The Haag Streit Pachometer

Honegger & Genee (1968) made a direct comparison between the instruments at present commercially available viz the Maurice Giardini pachometer the attachment to the Zeiss slit lamp (in a slightly modified form) and the attachment I to the Haag Streit slit lamp model 900 The latter showed the smallest measuring error and appears to be the most simple in use

During the last years we have worked with the Haag Streit pachometer in clinical and experimental studies In connection with the preceeding review of the optical principles for the measurement of corneal thickness we have found occasion to present some comments on the use of this pachometer

1 The apparatus and its use

The principle was given by *Juillerat & Koby* (1928) but it was particularly and independently developed by *Jaeger* (195?) (see section I 5 and fig 6) The apparatus consists of an attachment to the Haag Streit slit lamp containing two glass plates in front of the right microscope a lower fixed and an upper rotat

Fig 6

Measurement of the apparent thickness of the optical section The principle of *Jullcrat & Koby Jaeger* The light falls perpendicular onto the cornea The apparent optical section is measured from the side Indications as in fig 1

lar technically improved apparatus is now available for use with the Haag Streit slit lamp model 900 (Haag Streit Berne)

The optical section of the light falling perpendicular onto the corneal surface is observed at an angle of 40° In the microscope the image of the optical section is now seen The thickness of this is measured by aligning the anterior and the posterior corneal surfaces by means of a rotating plane parallel glass plate covering the lower half of the reflected light The calculation of the real thickness proceeds as in the method of *Blix* and *von Bahr* Substituting in equation (1) $d = a/\sin\lambda$ we have

$$x = r - \frac{r \sin\lambda - \frac{a}{\sin\lambda}}{n \sin(\alpha+\psi)} \qquad (3)$$

a is the displacement of the light caused by the glass plate and known from the angle of rotation (cf eq 2) The only unknown factor is therefore again $\sin(\alpha + \psi)$ which can be exactly calculated *Jaeger* provided for different values of r graphs showing the real thickness as a function of the displacement a Variation in r gave only minor variations in thickness In the attachment to the

if the patient looks into the light and this together with the position of the light in the pupil generally gives a sufficient localization

When the patient fixes the incident light the measurement is made along the line of sight and not along the perpendicular to the cornea This introduces a measuring error and a systematic difference between right and left eye

Some optical definitions As regards the different axis in the eye and the angles between them nearly every author uses his own definitions and in case of equal definitions often uses different symbols In the present connection we need to define the line of sight by which we understand the line in the optical system followed by the light ray to the fovea The localization of this in the optical system is unknown in the individual case and there is of course no reason to assume that it goes perpendicular through the center of the cornea The other line of interest is this line perpendicular through the center of the cornea along which we want to measure the corneal thickness

Clinically we can measure an angle here called kappa between the line of sight and a line perpendicular to the anterior corneal surface and going through the center of the apparent pupil Where these two lines intersect if they do so at all we do not know

During the use of the pachometer it was noted that often the corneal thickness was the greater in the left eye and in a material of normal eyes (*Kruse Hansen* 1971) a statistically significant difference could be demonstrated ($P < 0.001$) In fig 8 corneal thickness difference between the left and the right eye is plotted against the sum of the angles kappa of the two eyes A *linear regression* analysis showed significant correlation ($P < 0.001$ $R = 0.84$)

On the assumption that an angle kappa equivalates a decentered fixation the

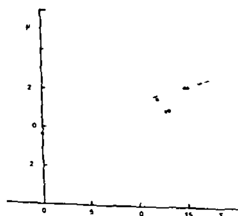


Fig 8
Corneal thickness difference between left and right eye plotted against the sum of the angles kappa of the two eyes Equation of regression $\Delta\mu = 1.6\Sigma K - 9.3$
abscissa = degrees ordinate = m^{-4}

able around a vertical axis The incident light comes through a vertical aperture in a diaphragm extending from the attachment and securing an angle of 40° between the incident light beam and the axis of the right microscope The right ocular is replaced by a special slit image ocular dividing the visual field into lower and upper halves The light passing through the upper rotatable and the lower fixed glass plates is seen in the upper and the lower visual field re spectively

In the microscope the optical section through the cornea is seen When the upper glass plate is rotated the upper part of the image of the optical section is displaced (fig 7) The angle of rotation of the glass plate is a measure of the corneal thickness (cf eqs 2 & 3) and is read on a scale directly calibrated in mm As mentioned in section I 5 a correction for variation in corneal curvature and non linearity is necessary This is obtained from a table supplied by Haag Streit This correction is numerically of minor importance except in cases of megalocornea keratoconus etc

An advantage of this apparatus over those using specular reflection from the corneal surfaces is the possibility of measuring total thickness stromal thickness (*Ehlers* 1970) or the depth of a stromal clouding or a vessel (fig 7c) This last will be of importance in planning lamellar keratoplasty With this principle the microscopic magnification does not influence the measurement (*Jaeger* 1952) and the greater objective magnification (x 1 6) may be recommended Likewise the refraction of the observer does not influence the measurement (*Goldmann* 1968)

2 The significance of the angle kappa

According to the optical principle the incident light should fall perpendicular to the cornea This is obtained by having the patient fix the incident light Be sides introducing the limitation that only central thickness can be measured this gives the possibility of certain measuring errors To the trained observer it is to some degree possible from the Tyndall reflection in the optical section to know

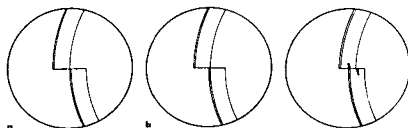


Fig 7

Diagrammatic illustration of the image seen in the ocular of the Haag Streit pacho meter a measurement of total corneal thickness b measurement of stromal thickness c measurement of the depth of an opacity

On a clinical material however a reduction of the standard deviation of the value for the central corneal thickness in a group of subjects is not evident (compare values of *Mishima & Hedbys* and *Kruse Hansen* 1971) An explanation of this may be the difficulty in fixing steadily a small target near to the incident light which seems necessary in the Mishima Hedbys modification

3 Measuring accuracy

When the accuracy of the measurement of the cornea is discussed it must be realized that the thickness varies with the thickness of the precorneal film This means that the cornea changes its thickness with 1 or 2 μ in the period between two blinkings This obviously rises the question what should be understood by the thickness This problem is in fact even greater as there is a priori no reason to assume that methods using specular reflections and methods based on observation of the optical section measure exactly the same distance of a given cornea

In the methods using measurement of the apparent thickness of the optical section the width of the slit lamp light and the focusing of the microscope will set a theoretical limit for the accuracy With the relatively low magnification used in the Haag Streit pachometer this is however no practical problem

Kruse Hansen (1971) made 5 determinations of the thickness in 37 subjects From this the statistical variance of the method may be calculated as the mean of the variances of the 5 readings Of course the variation in thickness during the period between two blinkings probably reduces the use of Gaussian statistics to a matter of convention The values obtained are $s_{d\ t} = 0\ 0085$ and s_s = 0 0079 Apparently there is no difference in the accuracy of the determination of the thickness of the right and the left cornea The mean value s_d = 0 008 mm may be given as the error of a single measurement This value is similar to that of *Honegger & Genee* (1968) and a little smaller than the values given by *von Bahr* (1948) and *Maurice & Giardini* (1951) for other instruments

Summary

The different principles used or proposed to be used in the optical measurement of the corneal thickness are reviewed and illustrated in diagrammatic form.

The measurement of the thickness of the apparent optical section of the cornea in the technical elaboration of the attachment to the Haag Streit slit lamp is simple in practice and appears to be the most accurate The error of the measurement (the standard deviation) is found to be 0 008 mm With this apparatus however a small but systematic difference between right and left eye may be demonstrated caused by the angle kappa between the optical axis of the eye and the line of sight.

effect of this was studied by use of a small movable fixation light on the diaphragm of the pachometer Fig 9 shows that a systematic variation occurs If the subject fixes to the left of the incident light too high values are obtained and if he fixes to the right too low values are found This systematic variation also observed by *von Bahr* (1948) probably corresponds qualitatively to the difference observed between right and left eye and as seen from the figures it is of a considerable magnitude The thickness difference caused by a given angle is not equal in the two diagrams This could be because in fig 9 the decentering occurs around the center of rotation of the eye whereas in fig 8 the decentering is caused by different optical errors in the eye A geometrical calculation of this error is for the same reason rather speculative and any attempt to make a correction for a measured angle kappa has not been performed

von Bahr (1948) also noted a difference between the right and the left eye caused by a systematic error of the method With his apparatus the right eye was found to be the thicker The two principles are however so different that no direct comparison is possible and no controversy exists

Mishima & Hedbys (1968) have introduced a modification of the pachometer with two small lights placed 40° to the left of the incident light (for the observer) If the light beam falls perpendicular onto the anterior corneal surface the reflection of these small lights will be seen aligned with the corneal epithelium This modification is theoretically correct and in addition makes a measurement of peripheral thickness possible

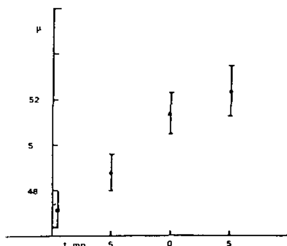


Fig 9

Systematic variation in the measured thickness when the incident light is not fixed exactly Right eye of subject with angle kappa O As the corneal area studied is within the approximately spherical optical portion of the cornea (*Berg* 1929 *Tscherning* 1924) no correction for change in corneal curvature has been performed
abscissa = degrees ordinate = m^{-6}

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Table I
Values of central corneal thickness as given in literature

Author	Corneal thickness (mm ± S D)	No of eyes	Year
von Bahr	0.565±0 035	224	1948
Maurice & Giardini	0.507±0 028	44	1951
Lavergne & Kelecom	0 51 ±0 04	198	1962
Donaldson	0.522±0 041	268	1966
Martola & Baum	0.523±0 039	209	1968
Mishima & Hedbys	0 518±0 02	40	1968
Lowe	0 517±0 034	157	1969

All measurements were performed according to the directions for use given by the factory

Each cornea was measured 5 times (*Honegger & Genee* 1968) the means were calculated and corrections for corneal curvature were performed when necessary The corrected mean values were used in the correlation studies

The radius of corneal curvature of each eye was measured with a Javal Schiotz keratometer (Haag Streit) and the intraocular pressure was measured

Table II
Material grouped according to age

Age (years)	No of subjects measured		
	Right eyes	Left eyes	Both eyes
10–19	6	8	6
20–29	9	6	10
30–39	3	6	4
40–49	3	3	6
50–59	5	6	1
60–69	5	4	6
70–79	6	4	4
80–89	o		
	39 eyes	37 eyes	37 pair of eyes

The Department of Ophthalmology (Head Prof Viggo A Jensen)
Kommunehospitalet University of Århus 8000 Århus C Denmark

A CLINICAL STUDY OF THE NORMAL HUMAN CENTRAL CORNEAL THICKNESS

BY

FINN KRUSE HANSEN

Since *Blix* (1880) as the first performed an optical measurement of the central corneal thickness several investigators have made similar measurements with various instruments but with grossly consistent results (*Ehlers & Kruse Hansen* 1971) Table I shows values of central corneal thickness obtained from greater materials

1964 the hitherto best instrument the Haag Streit pachometer (*Honegger & Genee* 1968) became commercially available

The purpose of this paper is to present the results of some biometrical studies with the Haag Streit pachometer and to discuss some of them

Material and Methods

150 eyes from 113 subjects (45 females and 68 males) were measured The 113 subjects were members of the hospital staff students and patients from the department of ophthalmology In many patients with unilateral diseases e g traumas the healthy contralateral eye was measured No subjects with corneal diseases were included The age distribution of the material appears from table II

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on the right than on the left side Finally in 6 subjects the values of right and left central corneal thickness were equal From these figures it can be shown by a simple sign test that the left cornea is significantly thicker than the right ($P \ll 0\ 01$) Further statistics are not needed

This side difference that seems to be due to the angle kappa causing a slight decentering of the measurement of central corneal thickness has been further discussed in another paper (*Ehlers & Kruse Hansen* 1971)

As a linear analysis of regression shows significant correlation between the right and left central corneal thickness ($P < 0\ 001$) only values from right eyes will be used in the following

Sex difference

The 76 right eyes were measured in 40 males and 36 female subjects The average central corneal thickness for male subjects was $0\ 519 \pm 0\ 018$ mm the corresponding figure for females was $0\ 520 \pm 0\ 019$ mm By a Student s *t test the* difference was demonstrated not to be statistically significant ($0\ 05 > P > 0\ 01$)

Age variation of central corneal thickness

The average central corneal thickness of all right eyes in various age groups appears from table III By an analysis of variance of these figures no statistically significant heterogeneity among the age groups could be demonstrated ($F = 2\ 21$ $f_1 = 6$ $f_2 = 69$ $P > 0\ 05$)

Table III
Mean values of central corneal thickness in various age groups 76 right eyes

Age (years)	10–19	20–29	30–39	40–49	50–59	60–69	>70
No of eyes	1	19	7	9	6	11	12
Average corneal thickness (mm)	0.5 5	0 513	0 511	0 527	0 516	0.524	0.525

Central corneal thickness and body height

The mean values of *right* central corneal thickness in 72 subjects older than 14 years appear from table IV An analysis of variance of these figures shows heterogeneity among the height groups significant at the 5 % level ($F = 3\ 78$ $f_1 = 3$ $f = 68$ $0\ 05 > P > 0\ 01$) Hovewer as Bartlett s test showed significant

by applanation tonometry Finally the refraction was determined and the body height was noted

Values are given as mean ± standard deviation

Results

The frequency distribution of central corneal thickness of the 76 right eyes appears from fig 1 By a probit test it can be shown not to differ significantly from the normal Gaussian distribution

Central corneal thickness – right versus left cornea

The average central corneal thickness of the 76 right eyes is o 520 ± 0 018 mm The corresponding value of the 74 left eyes is 0 524 ± 0 020 mm A statistical comparison of these values is not relevant as they include values from different subjects

In 37 subjects both eyes were measured 28 of these subjects had a thicker cornea on the left than on the right side whereas 3 subjects had a thicker cornea

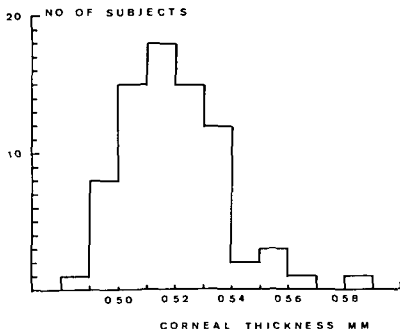


Fig 1

Histogram showing frequency distribution of central corneal thickness in 76 right eyes

on the right than on the left side. Finally in 6 subjects the values of right and left central corneal thickness were equal. From these figures it can be shown by a simple sign test that the left cornea is significantly thicker than the right ($P \ll 0.01$). Further statistics are not needed.

This side difference, that seems to be due to the angle kappa causing a slight decentering of the measurement of central corneal thickness, has been further discussed in another paper (*Ehlers & Kruse Hansen* 1971).

As a linear analysis of regression shows significant correlation between the right and left central corneal thickness ($P < 0.001$), only values from right eyes will be used in the following.

Sex difference

The 76 right eyes were measured in 40 males and 36 female subjects. The average central corneal thickness for male subjects was 0.519 ± 0.018 mm, the corresponding figure for females was 0.520 ± 0.019 mm. By a Student's t test the difference was demonstrated not to be statistically significant ($0.05 > P > 0.01$).

Age variation of central corneal thickness

The average central corneal thickness of all right eyes in various age groups appears from table III. By an analysis of variance of these figures no statistically significant heterogeneity among the age groups could be demonstrated ($F = 2.21$, $f_1 = 6$, $f_2 = 69$, $P > 0.05$).

Table III

Mean values of central corneal thickness in various age groups. 76 right eyes.

Age (years)	10–19	20–29	30–39	40–49	50–59	60–69	>70
No. of eyes	12	19	7	9	6	11	12
Average corneal thickness (mm)	[illegible]	0.513	0.511	[illegible]	0.516	0.524	0.525

Central corneal thickness and body height

The mean values of right central corneal thickness in 72 subjects older than 14 years appear from table IV. An analysis of variance of these figures shows heterogeneity among the height groups significant at the 5 % level ($F = 3.78$, $f_1 = 3$, $f_2 = 68$, $0.05 > P > 0.01$). However, as Bartlett's test showed significant

Table IV
Body height and central corneal thickness

Height (cm)	<160	160–169	170–179	>180
No of eyes	7	25	26	14
Average corneal thickness (mm)	0 530	0 522	0 522	0 508

inhomogeneity of the variances (χ = 18 86 P<0 0005) the analysis of variance is not valid

Intraocular pressure and central corneal thickness

All eyes were normotensive (range 8–18 mm Hg mean 13 7±2 1 mm Hg) The correlation between central corneal thickness and intraocular pressure of all

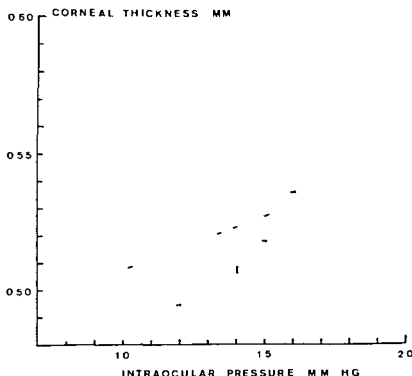


Fig 2
Correlation between central corneal thickness and intraocular pressure in 76 right eyes

right eyes appears from fig. 2. A linear regression analysis proved that the increase in thickness with increasing intraocular pressure was significant ($P < 0.001$).

Refraction

Many of the subjects were emmetropic and the refractive errors that were found were of minor degrees (– 4 to + 3). One myopic subject (– 5 both eyes) had a corneal thickness of 0.498 mm on the right eye and 0.500 mm on the left eye: the corresponding values of the only excessive myopic subject were 0.510 and 0.518 mm.

No attempt has been performed to evaluate a possible influence of refractive errors on central corneal thickness in the present material.

Anterior corneal curvature and central corneal thickness

A linear regression analysis showed no correlation between central corneal thickness and anterior corneal curvature.

Discussion

The normal frequency distribution of central corneal thickness in the present material is in good accordance with the findings of *Martola & Baum* (1968) and of *Mishima* (1968). It therefore seems correct to state that central corneal thickness of healthy subjects is Gaussian in distribution.

In the present material an average central corneal thickness of 0.520 ± 0.018 mm was found in 76 right eyes, the corresponding value of 74 left eyes was 0.524 ± 0.020 mm. This sidedifference, also noted by von Bahr, is caused by the angle kappa (*Ehlers & Kruse Hansen* 1971). The results are in good accordance with most earlier investigators (table I). The value of the present study is however only directly comparable with figures obtained by the same measuring technic. *Mishima & Hedbys* (1968) give a figure of 0.518 ± 0.02 mm of 40 eyes and Lowe (1969) found an average central thickness of 0.517 ± 0.034 mm in 157 eyes. These results are in excellent accordance with those of the present study.

Several authors have studied the influence of age on central corneal thickness (*von Bahr* 1948, *Lavergne & Kelecom* 1962 and *Martola & Baum* 1968). None of them however have demonstrated significant variations between different age groups in good accordance with the results of the present material.

The question of a possible correlation between central corneal thickness and body height, which may be presumed from table IV, cannot be answered from

the present material but will be studied later together with the possible effect of the refractive state

In the present study central corneal thickness increases significantly with increasing intraocular pressure within normal range this has apparently not been demonstrated before *Ehlers & Ruse* (1967) found a significantly increased corneal thickness in hypotensive eyes with retinal detachment *Ehlers* (1970) demonstrated a significantly decreased central corneal thickness in glaucomatous eyes during hypertensive phases These thickness variations with intraocular pressure will be further studied

Summary

Central corneal thickness was measured in 150 normal eyes with the Haag Streit pachometer A mean value of 0 520±0 018 mm was found in 76 right eyes whereas the value of 74 left eyes was 0 004 mm higher due to the angle kappa A normal frequency distribution is demonstrated Central corneal thickness is found to increase significantly with increasing intraocular pressure within normal range and possibly to decrease with increasing body height No correlation between age refraction and anterior corneal curvature was found No sexdifference was found

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From the Department of Ophthalmology Kommunehospitalet Copenhagen
(Heads P Brændstrup and M S Norn)

IODONITROTETRAZOLIUM VITAL STAINING OF CORNEA AND CONJUNCTIVA

BY

M S NORN

Tetrazolium salts are colourless substances which can be converted into coloured compounds by reduction This reaction takes place in the presence of a suitable substrate and a suitable enzyme (dehydrogenase lactase monoamino oxidase choline dehydrogenase etc) capable of liberating hydrogen from the substrate

Such enzymes are present in the mitochondria of the cells in certain bacteria (staphylococci coli) in germinating grain in malignant tissue etc

Tetrazolium salts have been used for instance as milk test (disclosing bacteria) as grain test (living grains become stained) and to demonstrate malignant tissue (*in vivo* and in preparations for microscopy) *In vivo* the substances have been employed for studying protozoa internal structures of the follicle mite and gastric dehydrogenase activity in rats and guinea pigs

Tetrazolium salt has also been used for studying the viability of the corneal disc in transplantation (Mueller Pakarinen and others) The disc is placed with the epithelial side downwards The cavity is filled with 0 1 % nitrotetrazolium and the preparation is incubated for 90 minutes Then follows fixation and microscopy Mueller interprets stained endothelial cells as a sign of impaired cell vitality

Staining of the cell presupposes first that the cell wall permeability is increased thus allowing tetrazolium to penetrate through the wall and secondly

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that the cell contains living mitochondria whose enzyme activity together with substrate in the cell can reduce tetrazolium to a coloured compound

In relation to beginning and progressive cell degeneration the permeability will increase and optimum mitochondrial activity be attained Increasing staining can accordingly be expected with progressive degeneration

Continued cell degeneration and finally cell death will yield optimum permeability while the enzyme activity will decline Therefore after a certain maximum the stainability must be expected to become reduced again

Accordingly tetrazolium staining is not direct comparable with vital staining using other dyes e g rose bengal with which increasingly intense staining indicates progressive cell degeneration and cell death

The object of the present investigation was to study for the first time the properties of a tetrazolium salt as a vital stain for the cornea and the conjunctiva in normal eyes and in a material of diseased eyes

Present Investigations

Different tetrazolium compounds exist e g tetrazolium blue which becomes reduced to blue diformazan and iodonitrotetrazolium which becomes reduced to red formazan The latter compound reacts more promptly and is less photosensitive than the former It has therefore been employed in the present investigation

The compound has the following formula

2 (p iodophenyl) 3 (p nitrophenyl) 5 phenyltetrazolium chloride (fig 1)

0 01 ml of 1 % iodonitrotetrazolium was instilled into the conjunctival sac Stainable regions presented increasing red colouring within the first few minutes with maximum after 3–4 minutes The result was therefore read in the slit lamp 4 minutes after the instillation The colour holding for several hours the time of reading after an interval of not less than 4 minutes from the instillation plays no decisive role.

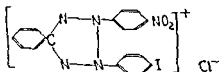


Fig 1
Iodonitrotetrazolium formula

Preliminary experiments showed that the inferior tarsal conjunctiva often was stained intensely, more so than is usual with other vital stains This might be due to iodonitrotetrazolium precipitating at the site of instillation (in the infero lateral conjunctival fold) In the main series I therefore chose to apply the drop on the bulbar conjunctiva above and lateral to the cornea with the patient looking down and nasally In this manner the compound was instilled within a region where staining practically never occurs and the significance of the site of instillation could be assessed

The staining results were entered in a diagram showing the kind extent site and degree of the staining

The staining degree was estimated arbitrarily in grades 1 to 5 3 indicates moderate staining 2 weak 4 intense 1 just visible and 5 maximum

Staining at the site of application on the bulbar conjunctiva was not included but was estimated separately

A total of 302 eyes of 205 subjects were examined The main material having had dye applied above and laterally on the bulbar conjunctiva comprised 273 eyes The diagnoses are seen in table 1

Result

The iodonitrotetrazolium staining manifested itself on the conjunctival and corneal epithelia as a group of very fine dark red dots often scattered but sometimes collected to form a pathological pattern The dots were smaller and the colour darker than after staining with rose bengal A stained dot was seen microscopically to consist of an accumulation of epithelial cells with red granules in the cytoplasm The nucleus remained unstained

In the total main material iodonitrotetrazolium staining was fairly frequent on the cornea bulbar conjunctiva and tarsal conjunctiva (25 32 and 25 per cent respectively) The plica semilunaris inferior fornix and Marx line on the other hand were more rarely stained (17 2 and 8 per cent respectively)

The caruncle was stained in 28 per cent This was a relatively lower percentage than by staining with rose bengal methylene blue and trypan blue (*Norn* 1970B)

The vital stains employed so far have the great disadvantage of staining certain normal regions in addition to pathological structures Marx line the caruncle and the plica semilunaris are often stained also in normal eyes by these usually employed dyes (Marx line is the conjunctival zone found along the ciliary margin bordering on the palpebral skin just behind the orifices of the meibomian glands)

Vital staining of the cornea and bulbar conjunctiva is generally of greater clinical interest The distribution of the iodonitrotetrazolium staining on the conjunctiva and cornea suggests that the compound preferably stains clinically relevant regions

Normal Eyes

The cornea was rarely stained in normal eyes (in 8 per cent of 59 eyes) The staining amounted to few dots only of grade 1 localized below and nasally or low on the cornea

The bulbar conjunctiva was stained in a somewhat greater number (table 1) In the whole normal material the grade of staining averaged 0 4 The staining was most often localized below and nasally

The other localities were rarely stained More particularly there is reason to point out that Marx line very rarely was stained (in 5 per cent) In this respect the compound differs definitely from 1 % rose bengal which stains the line distinctly often even intensely in all normal eyes (43 normal eyes *Norn* 1970B)

The cornea is likewise stained more frequently by rose bengal (40 per cent *Norn* 1970B) than by iodonitrotetrazolium (8 per cent)

Among the normals no age or sex difference was found regarding incidence or grade of iodonitrotetrazolium staining (on an average 11 per cent females and 16 per cent males showed staining in all seven examined regions)

Chronic Simple Conjunctivitis

This group comprised patients with pronounced conjunctival complaints through months often years without physical examination having disclosed any abnormality *I have been unable* so far to detect by vital staining any definite abnormality in relation to this disease (rose bengal fluorescein methylene blue trypan blue bromothymol blue alcian blue)

By vital staining with *iodonitrotetrazolium* just over one third of the patients with chronic simple *conjunctivitis* presented a remarkable punctate staining of the *tarsal conjunctiva* behind Marx line often comprising the central or nasal part of the tarsal plate covering most of the breadth of the tarsus

This staining was significantly more frequent among these patients than among normals ($0\,05 > p > 0\,02$) *Often* there was also seen punctate staining of the caruncle and the bulbar *conjunctiva*. The mean staining grade was 0 6 against 0 2 in the normal material

A similar frequent staining of the tarsal conjunctiva was only noticed within the groups of keratoconjunctivitis sicca and others

In keratoconjunctivitis sicca iodonitrotetrazolium also gave characteristic

Table 1

The percentage numbers of eyes stained by 1 % iodonitrotetrazolium in the region concerned (Others comprise vernal conjunctivitis ex ophthalmos ectropion obs *for infectious conjunctivitis* seventh nerve palsy dacryocystitis epiphora cataract extraction iritis subconj haemorrhage melanoma experimental lesions)

	number	cornea	bulb conj	plica	caruncle	inf fornix	tarsus	Marx line
normal eyes	59	9	31	8	22	2	14	5
chron simple conj	44	16	41	18	36	0	36	7
infectious conj	32	9	16	6	13	0	16	3
corneal disorders	31	55	13	16	16	0	13	3
contact lens wearers	9	11	67	22	22	0	22	11
keratoconj sicca	16	56	88	44	69	0	31	13
others	82	32	28	21	30	5	34	12
Total	273	25	32	17	28	2	25	8

staining of the cornea and bulbar conjunctiva a staining which was not seen in chronic simple conjunctivitis

The cases in the group of others possibly belong to the simple conjunctivitis group (tired eyes epiphora obs for infectious conjunctivitis)

Infectious conjunctivitis gave staining as in normal eyes

Corneal Disorders

In the cases of corneal disorders staining was seen at the site of the pathological process whereas the conjunctiva rarely was stained

Iodonitrotetrazolium was seen to stain marginal keratitis punctate keratitis dendritic keratitis erosion the area round a foreign body on the cornea corneal oedema tonometer injury etc Healed inactive keratitis was not stained

Contact Lens Wearers

Dying with iodonitrotetrazolium seemed to give relevant information disclosing corneal lesions and giving crescent staining corresponding to lens edge or intermediary curve

Keratoconjunctivitis Sicca

The exposed areas of the cornea and bulbar conjunctiva not covered by the eye lids were stained characteristically by iodonitrotetrazolium in the same manner as by rose bengal In some of the examined eyes weak staining was obtained also weak with 1% rose bengal

In *vernal* conjunctivitis punctate staining was occasionally seen round the bases of the papillae of the superior tarsus whereas never at their apices

In a case of *melanoma* at the corneal edge red staining was seen at the site of an ulceration and over the area round the ulceration constituting a limited portion of the tumour The greater part of the tumour on the other hand remained unstained

Experimental Lesions

Experimental lesions (tonometry gonioscopy filter paper introduced in the inferior fornix 4% cocaine on a cotton swab drill) seemed to be stained less effectively by iodonitrotetrazolium than by rose bengal the former having stained five and the latter nine out of eleven such lesions

Superior Tarsal Conjunctiva

In most cases vital staining was assessed without everting the upper lid

In 66 cases after double vital staining with 1 % iodonitrotetrazolium and 1 % rose bengal, I everted the upper lid and recorded the vital staining in this region

This study showed the conditions of the upper lid to correspond to those of the lower The superior tarsal conjunctiva was stained in many cases (42 per cent) most frequently in patients with chronic simple conjunctivitis (67 per cent against 17 per cent of normal eyes mean staining grade 1 3 against 0 2 in normal eyes)

No instance was found of iodonitrotetrazolium stained Marx line

The reverse was the case after dying with rose bengal The superior tarsal conjunctiva was stained in no more than 6 per cent whereas Marx line was stained in 63 per cent of the 66 eyes examined

Staining at the Site of Instillation

Instillation of *iodonitrotetrazolium supero temporally on the bulbar* conjunctiva gave staining of the primarily touched area in 26 per cent The staining limited to the "point of impact" manifested itself by a group of dots most often of a fairly weak grade The staining was equally frequent in normals and most of the pathological groups Only in the group of infectious conjunctivitis was staining at the site of instillation rarer than among normal eyes (9 per cent $p < 0.05$ Staining grade 0 1 against 0 5 in the normal group and 0 4 in the total material)

Double Staining

Rose Bengal

In 82 cases dying with iodonitrotetrazolium and reading of the result was followed by additional dying with 1 % rose bengal This procedure rendered possible *direct comparison of the two vital stains on a mixed clinical material* The result is shown in fig 2

Iodonitrotetrazolium was found to stain significantly less often than rose bengal in the following regions bulbar conjunctiva (35 per cent rose bengal 68 per cent) plica (23 per cent rose bengal 65 per cent) caruncle (30 per cent rose bengal 83 per cent) Marx line (10 per cent rose bengal 100 per cent)

The cornea was stained by iodonitrotetrazolium in 38 per cent and by rose bengal in 44 per cent The difference is not significant

The inferior tarsal conjunctiva was stained in 27 per cent of the eyes by iodonitrotetrazolium and in 17 per cent by rose bengal *The difference is not significant*

Iodonitrotetrazolium was thus seen to differ on essential points from rose

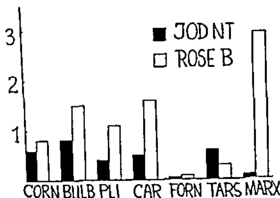


Fig 2

Mean staining grade in seven different regions after vital staining with 1 % iodonitrotetrazolium (black columns) and 1 % rose bengal (white columns) Double staining of 8? eyes Abscissa site Ordinate staining grade (arbitrary graduation 1 to 5)

bengal With the former one avoids the uncharacteristic staining of Marx line caruncle and plica which seem rarely to be of any clinical importance while on the other hand a fairly reliable staining of the cornea is obtained

In 19 cases the cornea was stained by both rose bengal and iodonitrotetrazolium in 12 only by iodonitrotetrazolium and in 17 only by rose bengal

Rose bengal alone disclosed cases of corneal lesion due to contact lenses lagophthalmos and corneal blisters while iodonitrotetrazolium alone disclosed cases of soda dye corrosion filiform keratitis etc

Regarding the bulbar conjunctiva some cases were found in which the crescent punctate staining under the cornea of contact lens wearers was most intense after instillation of iodonitrotetrazolium while in other cases rose bengal gave the strongest colour

Marx line was only stained by iodonitrotetrazolium in cases in which more intense staining was obtained by rose bengal

Fluorescein

In 82 cases additional dying was performed with fluorescein In 11 cases the cornea was only stained by fluorescein in 14 only by iodonitrotetrazolium and in 16 cases by both

Unlike tetrazolium fluorescein disclosed cases of contact lens lesion mild marginal keratitis and presence of foreign body while iodonitrotetrazolium

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Iodonitrotetrazolium was thus seen to differ on essential points from rose

In the other case a corneal suture canal was stained maximally immediately after removal of the suture The needle shaped red crystals in the canal gradually faded but were still just visible of a very pale colour some months later

In both cases it was a question of red crystalline precipitates in the subepithelial connective tissue

Use of iodonitrotetrazolium on non epithelium covered deep lesions especially such on the cornea or other visible region must therefore be contraindicated The same is true with regard to alcian blue which may cause a similar tattooing (*Norn* 1964A)

Using iodonitrotetrazolium a colourless fluid is instilled into the eye One thereby avoids discoloration of eyelid cheek fingers etc. as may occur when other vital stains are instilled

None of the patients complained of smarting on instillation of iodonitrotetrazolium Otherwise with rose bengal which caused irritation in several eyes

The iodonitrotetrazolium fluid had not lost its staining property after use over a period of more than six months

Discussion

The present investigation showed that iodonitrotetrazolium can be used for vital staining of the cornea and conjunctiva Its staining properties differ essentially from those of the generally employed vital stains

The regions that are stainable by iodonitrotetrazolium do not correspond exactly to those stainable by rose bengal for instance Thus Marx line the caruncle and the plica become stained in relatively few cases only whereas the cornea fairly often is stained From a clinical aspect this is a rather favourable distribution as one thereby often avoids colourings also seen in normal eyes and accordingly of no clinical importance

On the other hand we must admit that morbid conditions more often are stained by rose bengal The difference is not significant on comparing 1 % rose bengal with 1 % iodonitrotetrazolium whereas use of 10 % rose bengal shows a marked difference the latter staining a maximum of pathological structures (*Norn* 19,0B)

However at the same time staining with 10 % rose bengal involves more unnecessary normal staining and consequently a considerable risk of over diagnosing Using 1 % iodonitrotetrazolium on the other hand under diagnosing may occur in rare cases

The water solubility of iodonitrotetrazolium is fairly low and a higher concentration than 1 % is hardly of use for vital staining

alone disclosed cases of keratoconjunctivitis sicca and keratitis in the healing phase

In one case iodonitrotetrazolium fluorescein and rose bengal were instilled immediately after removal of a foreign body from the cornea The deep erosion caused by the foreign body was stained by fluorescein while the edge of the erosion and a zone round this was stained intensely by rose bengal Iodonitro tetrazolium stained only parts of the erosion edge and parts of the surrounding zone

Alcian Blue

Alcian blue is a mucus specific dye *(Norn* 1964A) 14 eyes were stained by both dyes mucous regions a bluish green colour contrasting distinctly with the red colour produced by iodonitrotetrazolium

Marx line was stained greenish blue and the tarsal conjunctiva sometimes red *In keratoconjunctivitis sicca most regions displayed both red and greenish* blue dots

The two dyes will even when mixed continue to stain different structures bluish green or red

Trypan Blue

Trypan blue stains exclusively dead cells and mucus *(Norn* 1967B 1969) Seven eyes were examined In general no merging was seen of regions stained red and regions stained blue by trypan blue In some cases a blue stained Marx line was seen and behind this a red stained tarsal conjunctiva

Side-effects

Vital staining with iodonitrotetrazolium is fairly stable While the colours pro duced by rose bengal and other vital stains fade considerably after 10 to 20 mi nutes that brought about by iodonitrotetrazolium may last for hours It will sub side in the course of less than 24 hours The stability is an advantage where de monstration of a patient is desired but is perhaps inconvenient for the patient himself

Permanent staining (tattooing) was noticed in two cases In one case the patient had a deep central corneal ulcer which was stained maximally with red crystals in the parenchyma The colour faded to the lowest grade in the course of some weeks

tion presumably by adding to the permeability of the cell membrane and at the same time stimulating the enzyme activity in the cytoplasm

In some cases the mucous thread in the inferior fornix assumed an intense red colour while in others only few dye granules were seen in an otherwise clear colourless mucous thread This phenomenon will be subjected to further study

Iodonitrotetrazolium has the great disadvantage that its use sometimes is contra indicated because deep parenchymatous lesions tend to become permanently stained Moreover in the cases that are not particularly pronounced under diagnosing may be feared

For ordinary clinical use the mixture of 1 % rose bengal and 1 % fluorescein introduced by the author (*Norn* 1964C) will perhaps still be preferred provided one is able to distinguish exactly between normal and pathological vital staining (*Norn* 1970A and B) On the other hand iodonitrotetrazolium is preferable in special cases e g for assessing chronic conjunctival complaints (chronic simple conjunctivitis)

Most vital stains have the same properties as rose bengal (merbromine scarlet red eosin Congo red) as they stain degenerate cells and mucus A few vital stains have differing specific properties fluorescein stains broken continuity of the epithelium trypan blue dead cells alcian blue only mucus and Sudan III only fat

To this list *of specific vital stains may now be added iodonitrotetrazolium* which stains *epithelial cells in a certain degenerative phase* In this phase the permeability of the cell wall is increased allowing the compound to penetrate and at the same time an appreciable enzyme activity is found in the cell mitochondria causing the colourless iodonitrotetrazolium to be reduced to the red formazan

Thus we cannot expect staining by iodonitrotetrazolium if on one hand the cell is alive and quite normal or if on the other hand the cell is dead or so degenerate that its enzyme activity is reduced

The compound differs in this respect from rose bengal for instance which stains with increasing intensity the more degenerate the cell with maximum colour intensity of the dead cell (cf *Norn* 1970B)

Summary

Vital staining of 30? eyes of 205 patients showed the colourless 1 % iodonitrotetrazolium to stain pathological corneal and conjunctival structures red (Keratitis erosion oedema contact lens wearers keratoconjunctivitis sicca corrosion etc)

Iodonitrotetrazolium constitutes an elegant solution of the vital staining problem a colourless fluid being instilled which stains mainly pathological structures alone and to a suitable extent

The compound is of particular interest in that staining of the inferior and superior tarsal conjunctivae seems to give unprecedented valuable information staining of this region raising suspicion of chronic simple conjunctivitis

There is reason to suppose that *chronic simple conjunctivitis* constitutes a heterogeneous group of affections comprising cases of conjunctival neurosis incompetence of conversion refractive anomalies proper conjunctival disorders etc

In the series under review it was for the first time possible to demonstrate an abnormality in a number of these patients namely vital staining of the superior and inferior tarsal conjunctivae by iodonitrotetrazolium a phenomenon never observed after instillation of other vital stains

The finding suggests a conjunctival abnormality within a special region the nasal or central part of the tarsal plate The epithelium is abnormal The staining is perhaps due to increased permeability of the cell wall and perhaps an increased enzyme activity in the mitochondria of this region

This observation in the individual patient after vital staining may perhaps bear out the diagnosis of simple chronic conjunctivitis in a restricted sense while failing iodonitrotetrazolium staining of the tarsus calls for further examination

The possibility might be conceived that the intensified staining might be due to precipitation of the dye similarly as is the case with methylene blue

Microscopy of vital stained scraped off epithelium showed however that the colour is derived from red granules in the cytoplasm of the epithelial cells Such coloured cells are found scattered or in groups among colourless epithelial cells No precipitated dye granules have been observed outside the cells

The staining of the tarsal conjunctiva must accordingly be characterized as genuine

It is remarkable that iodonitrotetrazolium occasionally causes staining at the *site of instillation* A similar source of error has been noticed for 10 % rose bengal Therefore by applying these dyes on the inferior tarsus one runs a risk of counting staining of the inferior tarsus as pathological To avoid this source of error instillation in a region which normally remains unstained (the bulbar conjunctiva) is required

Where 10 % rose bengal is concerned the phenomenon may be explained in the manner that the highly concentrated smarting dye remains for so long at the site of instillation before being diluted by conjunctival fluid that the subjacent normal cells become damaged

In the case of iodonitrotetrazolium the phenomenon is more difficult to explain This is a 1 % solution which seems to cause no irritation Nevertheless the compound will in some cases stain normal epithelial cells at the site of instilla

From the Department of Ophthalmology
Maulana A ad Medical College and Associated Irvin & G B Pant Hospitals
New Delhi – India

HEREDITY IN DUANE S SYNDROME

BY

PREM SINGH and BIJOYANANDA PATNAIK

The name Duane s syndrome applies to a group of anomalies of horizontal ocular movement characterised by a complete or less often partial loss of abduction partial or rarely complete loss of adduction There may be an associated upshoot or downshoot of the affected eye in adduction The eyes are orthophoric esophoric esotropic or rarely exotropic in primary position Parallelism in primary position is maintained by adopting a head posture usually with face turn to the side of maximal limitation The degree of deviation is disproportionately small as compared with the limitation of *movements* There is a narrowing of palpebral fissure with the retraction of the globe when the eye is moved against the direction of maximal limitation and a widening of fissure with protrusion of the globe when it is moved toward the main limitation These palpebral changes though form a very strinking feature of the syndrome are seen only in 50 % of the cases The syndrome is seen as a sporadic occurance in 90 % (*François* 1961) but occasionally cases with hereditary involvement are seen *Danis* (1948) could find only 62 instances of hereditary involvement out of 2/7 cases he reviewed One family with involvement in two generations is being reported

Case I

R N 23 yrs old Hindu male had a history of constant convergent squint since birth

There was no abnormal head posture In the primary position he had a left

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Normal regions are stained much less frequently than by 1 % rose bengal for instance (Marx line caruncle plica semilunaris)

36 per cent of cases of chronic simple conjunctivitis showed abnormal staining of the tarsal conjunctiva a phenomenon which has not been noticed using other vital stains

The dye remains in the epithelium for several hours The dye should not be used in the presence of deep corneal lesions owing to a risk of permanent tattooing

The staining properties of iodonitrotetrazolium have been compared direct with those of rose bengal fluorescein trypan blue and alcian blue

The conclusion has been drawn that iodonitrotetrazolium is a specific vital stain having other properties than the dyes employed so far The compound only stains epithelial cells with enzymatic activity

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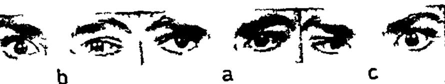


Fig 2

a) Right hypertropia in primary position b) On dextroversion Gross limitation of right eye with widening of right palpebral fissue and narrowing with enophthalmos of left eye c) On levoversion gross limitation of left eye with widening of left palpebral fissue and narrowing of right palpebral fissue with gross enophthalmos

and slight head tilt to the right He was showing a right convergent squint of 30 The right palpebral fissure was narrow and the eye was enophthalmic There was a gross limitation of the abduction in each eye with slight restriction of adduction in the right eye Each eye showed widening of the palpebral fissure and protrusion of the globe on abduction and narrowing of the palpebral fissure with retraction on adduction only in right eye (Fig 3)

The anterior segments were normal The visual acuity in the right eye was counting fingers from half a meter which did not improve with glasses The left eye was having a vision of 6 6 The ocular fundi were normal The fixation was paracaecal in right eye and central in left eye

Case IV

D D ?0 yrs old female (sister of the propitus) had no abnormal head posture



Fig 3

a) In primary position right convergent squint and narrow right palpebral fissure with slight enophthalmos b) On dextroversion gross limitation of right eye with widening of palpebral fissure and protrusion of globe c) On levoversion gross limitation of left eye Narrowing of palpebral fissue and retraction of globe right eye

Examined on home visit at Agra India

convergent squint of 20° with right hypertropia of 15° There was a gross limitation of abduction in each eye The limitation was more marked in the left eye. The left eye showed a downshoot in adduction Each eye showed widening of the palpebral fissure with protrusion of the globe on attempted abduction In adduction there was narrowing of the palpebral aperture with retraction of the globe only in the left eye (Fig 1)

The anterior segments were normal The visual acuity in the right eye was 6/5 and counting fingers at 1 meter in the left eye which could not be improved with glasses The ocular fundi were normal The fixation was central in right eye and paracoecal in left eye There was no binocularity

Case II

A K 17 yrs old male (the younger brother of the propitus) presented with a *constant squint of the left eye since birth He had no other complaints*

The patient had no abnormal head posture In the primary position he showed a left divergent squint of 2° with right hypertropia of 10° He could fix only momentarily with the left eye There was gross restriction of abduction of both eyes They could not move beyond the midline Each eye showed widening of their palpebral fissure with protrusion of globe of attempted abduction and narrowing of the palpebral aperture with enophthalmos on adduction (Fig 2)

The anterior segments were normal The visual acuity in the right eye was 6/9 which improved to 6/6 with -0 75 D sph The vision in the left eye was however 3/60 improvable to 6/36 with +0 75 D cyl axis 90° The ocular fundi were normal in both the eyes There was no binocular function

Case III

R K 11 yrs male (younger brother of the propitus) had a face turn to the left



Fig 1

a) Left convergent squint with right hypertropia in primary position b) On dextroversion gross limitation of right eye with right hypertropia and narrowing of left palpebral fissure c) On levoversion gross limitation of left eye with slight widening of palpebral fissure and protrusion of globe

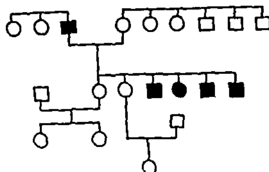


Fig 5
Family tree.

that the dominant eye was left in case I II and IV and right in case III In the reveiwed families no regular pattern of involvement was observed In some the same eye was involved in all the members while in the others either the left or the right or both the eyes were irregularly affected Some of the affected members in a family may have a classical picture of the syndrome while others may present an atypical or incomplete form Form Frustes of *François & DeVos* (1958) However the affected member of this family were showing the typical involvement

Summary

A family of Duane s Retraction syndrome with involvement in two generation is reported Informations on twenty eight such families have been presented on a review of the literature

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There was left hypertropia of 5° There was limitation of each eye in abduction and downshoot with narrowing of palpebral fissure in adduction (Fig 4)

***Case V**

R N 65 yrs old male (father of the propitus) was showing no abnormal head posture He had a right convergent squint There was a gross limitation of the right eye on abduction and retraction of the globe with narrowing of palpebral fissure on adduction

The third generation (three girls) progeny of the unaffected sisters of the propitus did not show any involvement None of the affected member is married

Discussion

Out of twenty seven cases of Duane s syndrome examined during one year there was a family in which the father and four (three males and one females) of his six children were affected indicating an autosomal dominant transmission to the second generation (Fig 5) Absence of involvement in the offspring of the unaffected members further support the contention that the anomaly is transmitted as an autosomal dominant trait In a review of twenty eight families of Duane s syndrome (summarised in table I) one generation was affected in sixteen families and three generations in seven families

Except for the father all other affected members of this family had bilateral involvement They were presenting a highly similar picture but for the fact

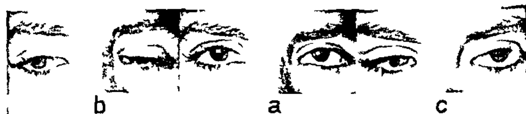


Fig 4

a) Orthohoria in primary position b) On dextroversion limitation of right eye and narrowing of left palpebral fissure c) On levoversion gross limitation of left eye and narrowing of right palpebral fissure

* Examined on home visit at Agra India

18 Bohringer	1952	III	2	2	4	Mother one son one daughter and grandson
19 Waardenburg	1953	III	4	1	5	Boy his mother maternal grandfather one uncle and one of the three sons of the uncle All had R E affected
20 Weeker et al	1955	II	1	1	2	Mother and child
21 Gedda and Magstretti	1956	II	–	4	4	Both MZ female twins their sister and mother L F affected in all
22 François	1957	II	6	3	9	Father and eight children out of ten (five sons and three daughters)
23 François	1961	II	–	3	3	Daughter sister and grandmother
24 François	1961	II	1	2	3	Woman her nephew and niece
25 Waardenburg	1963	III	2	1	3	One son of normal couple younger sister of the mother and their father
26 Waardenburg	1963	II	–	2	2	Two sisters and the mother
27 Waardenburg	1963	II	–	2	2	Mother and daughter
28 Waardenburg	1963	I	–	2	2	Discordand DZ female twin out of eight sibs

Table I

Author		No of generations affected	Affected Members			Description of the affected family members
			M	F	Total	
1 Heuck	1879	II	2	2	4	35 years old woman 2 sons and one daughter
2 Turk	1896	III	2	3	5	Father (R E) three daughters (L E) and a grandchild (boy) bilateral
3 Turk	1899	I	1	1	2	Two out of four children one brother and one sister
4 Varese	1901	II	1	1	2	Mother (L E) and the son (R E)
5 Wolff	1901	I	1	2	3	Three out of seven children one sister and brother (L E) *both eyes in one sister*
6 Kraus	1905	II	1	1	2	Mother and son
7 Endelman	*1911*	*II*	–	2	2	*Mother (L E) and daughter (L E)*
8 Peters	1921	I	–	–	–	Details of the affected members not available
9 Waardenburg	1921	II	2	2	4	Father two out of three daughters and one out of five sons Left eye affected in all
10 Gifford	1926	II	1	1	2	Mother (L E) and son (B E)
11 Waardenburg	1932	II	–	2	2	Mother (B E) and daughter (R E)
12 Lodberg	1935	II	–	2	2	Girl (B E) and her maternal aunt (L E)
13 Zentmayer	1935	III	1	2	3	Child mother and maternal grandmother
14 Laughlin	1935	III	1	3	4	Mother two sons one daughter and a grand daughter
15 Streiff and Zwahlen	1947	II	1	2	3	*Woman her brother and daughter*
16 Walsh	1947	II	–	2	2	Mother (L E) and daughter (L E)
17 Malbran	1949	III	2	2	4	*Two brothers mother and maternal grandmother*

18 Bohringer	19..	III	?	2	4	Mother one son one daughter and grandson
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27 Waardenburg	1963	II	–	2	2	Mother and daughter
?8 Waardenburg	1963	I	–	2	2	Discordand DZ female twin out of eight sibs

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Department of Ophthalmolo‿ Karolinska sjukhuset
104 01 Stockholm 60 Sweden

HUMAN RETINAL VASCULAR OBSTRUCTIONS

A quantitative correlation of angiographic and electroretinographic findings

BY

SVEN ERIK G NILSSON

Since the early work by Karpe (16) it has been known that patients suffering from obstruction of the central retinal vessels generally show a *pathologically* altered ERG In most cases the ERG was found to be negative or *subnormal* However supernormal normal and extinguished electroretinograms were also seen Classification of the patients according to type of ERG proved to be a good basis for prognostic judgements The prognosis was best among patients with supernormal normal and negative + ERG and gradually got worse with negative – subnormal and extinguished ERG (Karpe (16) Henkes (13 14) Karpe & Germanis (19)) The finding that visual acuity does not parallell ERG *completely* is easily explained by the fact that a minor haemorrhage in the *central* part of the macula seriously affects visual acuity but does not affect the remaining part of the retina It seems likely that the different types of ERG are expressions of *different* degrees of vascular obstruction The aim of the present investigation was to *determine* in the acute phase of the disease the degree of obstruction of the central retinal vessels using fluorescein angiography and to correlate these findings to the *size* of the different potentials of the ERG Since it was of interest to study not only the b wave but also the a *wave* the ERG was recorded over various intensities of light from the threshold for obtaining

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the scotopic b wave and to six logarithms above threshold The intention was to classify if possible arterial and venous obstructions together in the same system.

There are several reasons for doing a quantitative study of this kind It provides a possibility of studying further the morphological basis of the ERG It is well known that the retinal receptor cells get their main blood supply from the choroid and that the remaining part of the retina is supplied from the retinal vessels (Fig 1) Also there is much evidence that the a wave is generated in the receptor cells and the b wave in more vitreally located neurons (Granit (12) Arden & Brown (1), Brown & Wiesel (7) Brown & Watanabe (4 5) Brown Watanabe & Murakami (6) and Nilsson & Crescitelli (21 22)) Thus from an experimental point of view an obstruction of the retinal circulation ought to reduce the b wave whereas the a-wave should not be reduced primarily This is in accordance with the findings in the present investigation that the maximum a wave was generally not affected by obstruction of the central retinal vessels Furthermore a new principle for treatment of central retinal vein thrombosis has given promising preliminary results (2 3) The agent Reptilase is acting as a defibrinator thus inducing an endogenic fibrinolysis ERG and angiography ought to be of great value in order to select patients suitable for treatment No doubt some retinas are irreversibly damaged and there would be no hope for a successful treatment of these cases

Material and Methods

Based on a normal material of 26 eyes four cases of central retinal artery obstruction (CAO) and six cases of central retinal vein obstruction (CVO) were studied Of the ten cases eight were male and two were female The age ranged from 52 to 77 years with a mean of 60 6 years All patients were subjected to routine eye examination angiography as well as to ERG within a week after the onset of symptoms in most cases within four days In order to assure a proper comparison between the diseased eye and the fellow eye only patients with a healthy fellow eye (or with very minor hypertensive changes of the vessels) were included in the study

Fluorescein angiography of the retinal vessels (Novotny & Alvis (23)) was performed using a Zeiss fundus camera fitted with appropriate filters a motorized Robot camera and a Zeiss rapid sequence electronic flash generator

Five ml of 10 % sodium fluorescein was rapidly injected through a forearm vein Beginning about 8 seconds thereafter serial photographs were taken of the eye ground at intervals of approximately one per second (0 5–1 5 seconds) The time intervals were directly recorded by photographing a speedometer clock in a



Fig 1

l ght m ograph of human ret na C choroid R receptor cells O outer plexiform layer B bip lar cell layer I inner plexiform layer G ganglion cells A axons The thicker arrows indicate capillaries n the retina × 650

the scotopic b wave and to six logarithms above threshold The intention was to classify, if possible arterial and venous obstructions together in the same system

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2a

2b

2c

2d

Fig 2

Flu esce n angiogram of a normal eye Fluorescein just beginning to enter retinal teries at 15 sec (Fig ?b) Lam nar flow in the main vein branches begins at 17 5 sec (Fig ?c) Retinal circulation time 2 5 sec

corner of the film negative (Fig 2) The arm – to – retina time is the interval from injection to the first appearance of fluorescein in the retinal arteries The retinal circulation time is defined as the time interval between the first appearance of fluorescein in the retinal arteries and the first appearance of fluorescein as a laminar flow along the walls of the retinal veins

Fig 2 shows some photographs from a sequence of pictures of a normal angiogram In Fig 2a (14 sec) no fluorescein is seen At 15 sec (Fig 2b) some arteries are slightly lighter than in the preceeding picture indicating that fluorescein is just approaching the retinal arteries In Fig 2c (15 5 sec) the arteries are filled with fluorescein The arterial fluorescence is more intense in Fig 2d (16 5 sec) Laminar flow of fluorescein in the main vein branches is evident in Fig 2e (17 5 sec) and in Fig 2f (19 sec) The arm – to – retina time was in this cas 15 sec and the retinal circulation time 2 5 sec The best accuracy that could be obtained in this material was ± 0 5 sec Eleven normal eyes (eight male and three female) were investigated as a control The arm – to – retina time varied from 11 to 31 5 sec with a mean of 18 5 sec The retinal circulation time varied from 1 5 to 3 sec with a mean of 2 2 sec figures well in accordance with those reviewed by Wessing (33) Mean and standard error (S E) for the circulation times are found in Table I

The electroretinographical examination was initiated with a period of semi dark adaptation according to Karpe (17) Mydriacyl® and 10 % Neosynephrine® was used for dilatation of the pupils The stimulus light was a special electronic flash lamp described by Karpe & Algvere (18) The visual angle of the light stimulus was approximately 90° For a pupil diameter of 8 mm the light intensity was about 33 000 Lux Neutral filters were used for reduction of the light intensity in a logarithmic manner The unattenuated intensity is regarded as reference level and is referred to as log relative intensity 0 An intensity attenuated to 1/10 is referred to as log relative intensity –1 (log 10 0 1) etc The interval between the flashes was made sufficient to maintain the state of dark adaptation According to Karpe (16 17) the potentials were led off through a contact glass electrode (Sundmark s model 29) the indifferent electrode being placed on the forehead The potentials were fed into a condenser coupled amplifier with a time constant of 2 5 seconds

Fig 3 shows a sequence of normal ERG recordings with light intensities from log –6 (Fig 3a) (just above threshold for obtaining a recordable scotopic b wave) to the unattenuated flash intensity (Fig 3g) (same patient as in Fig 2) Calibration 0 50 mV and 100 msec In the records the stimulus artefact is seen to preceed the potentials of the ERG With increasing light intensity the a wave is increasing throughout the series The b wave is first increasing and then decreasing The B wave (measured as the perpendicular distance between the bottom of the a wave and the top of the b wave) is increasing although at different rates in different parts of the series A decrease in implicit time for the

Table I

Range mean and S E of the maximum ERG potentials (mV) of 26 normal eyes and of circulation times (sec) for 11 normal cases

	ERG			Arm to retina time	Retinal circulation time
	a	b	B		
Range	0 37 – 0 61	0 ?7 – 0 66	0 46 – 0 96	11 0 – 31 5	1 5 – 3 0
Mean and S E	0 47 ± 0 01	0 44 ± 0 0?	0 ?0 ± 0 03	18 ?± 1 7	?2 ± 0 1

a wave as well as for the b wave is easily noted In several patients the curves were distorted due to eye movements and blinkings To these patients Van Lint anaesthesia was applied The reflex blinkings caused by the strong stimulus *light if present did not distort the ERG curve until after the top of the b wave* The negativity seen after the b wave in records e f and g might at least partly repres nt remaining negativity belonging to the negative receptor potential I ig 3h shows for comparison the patient s routine ERG at maximum b wave (80 Lux)

Normal eyes

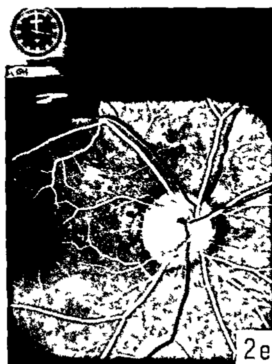
Range mean and standard error (S E) of the maximum ERG potentials of 26 normal eyes (16 male and 10 female) are listed in Table I In Figs 12–14 the amplitude of the potentials are plotted against light intensity

Observations on pathological cases

Cases of obstruction of the central retinal vessels are generally divided into two groups central artery obstruction (CAO) and central vein obstruction (CVO)

Fig 3

N rmal electro etinogram recorded with light intens ties from just above threshold for the scot pic b wave (Fig 3a) up to ? log units above threshold (Fig 3g) I = log rela ti e ntens ty Maximum b wave at log relative intensity –4 (Fig 3) Maximum a wave n l B wa e at unattenuated ntensity (Fig 3g) Fig 3h Routine ERG at maximum b wave (80 Lux) Top recording right eye Calibrat on 0 50 mV and 100 msec (valid also for the following records)

















Cal.

I=-6
3a

I=-5
3b

I=-4
3c

I=-3
3d









I=-2
3e

I=-1
3f

I=0
3g

3h

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Cases of obstruction of the central retinal vessels are generally divided into two groups central artery obstruction (CAO) and central vein obstruction (CVO)

Fig 3

N rmal electroretinogram recorded with l ght intensities from just above threshold for the sc topic b wave (Fig 3a) up to 6 log units above threshold (Fig 3g) I = log rela ti e intens ty Maximum b wave at l g relative intensity –4 (Fig 3c) Maximum a wave and B wav at unattenuated intensity (Fig 3g) Fig 3h Routine ERG at maximum b wave (80 Lux) Top recording right eye Calibration 0.50 mV and 100 msec (valid also for the following records)

2e

2f

Cal.

I=-6
3a

I=-5
3b

I=-4
3c

I=-3
3d

I=-2
3e

I=-1
3f

I=0
3g

3h

Table II

Cases of CVO and CAO with *ERG potentials within* the normal range and with a difference from the fellow eye not exceeding 25 % = successful cases

	ERG						Arm to retina time sec	Retinal *circulation* time sec
	a		b		B			
	mV	Diff %	mV	Diff %	mV	Diff %*		
CVO ♂	0.43	+13.7	0.38	+13.9	0.57	+ 5.8	14.0	4.5
CVO ♂	0.47	+ 6.4	0.41	+14.6	0.66	+16.7	16.5	3.5
CVO ♀	0.38	± 0	0.27	−12.9	0.51	+ 9.8	17.0	4.5
CVO ♂	0.51	− 1.9	0.40	−13.0	0.83	+ 4.8	15.0	4.0
CAO ♂	0.40	− 2.4	0.55	−14.1	0.67	− 7.5	20.5	4.5
Mean ± S E	0.44 ± 0.07		0.40 ± 0.05		0.63 ± 0.06		16.6 ± 1.1	4.2 ± 0.2

* Difference in amplitude from the fellow eye calculated as per cent of the maximum potential of the eye with the greater amplitude. If the potential with the greater amplitude belongs to the diseased eye this is indicated as +. The reversed is indicated as −. The same thing is valid for Table III

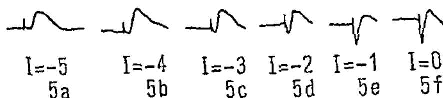
For the purpose of the present investigation which aims at correlating the amplitudes of the potentials of the ERG to the retinal circulation time it soon became obvious however that a grouping in successful cases and unsuccessful cases" (see below) each group including CAO as well as CVO was more appropriate

In table II cases of CVO and CAO with ERG potentials within the normal range and with a difference from the fellow eye not exceeding 25 % = "successful cases are listed Representative examples of angiograms and electroretinograms of such cases are shown in Figs 4–7 Although the amplitude means of the a b and B potentials were slightly below those of normal cases the difference was not statistically significant The difference from the fellow eye which sometimes went in favour of the diseased eye and sometimes in favour of the healthy eye seemed to be of no value as a way of distinguishing between normal eyes and the eyes of this group The retinal circulation time was significantly longer (at the 1 ‰ level) than that of the normal cases The mean difference was only two seconds however

Table III lists cases of CVO and CAO with b potentials below normal range and with a difference from the fellow eye exceeding 25 % = "unsuccessful cases" Representative angiograms and electroretinograms of this group are shown in Figs 8–11 The mean of the a wave amplitude did not significantly differ from that of normal cases or from that of successful cases In one case (second of Table III) of all cases listed in Tables I–III there was a marked difference between the two eyes as to a wave amplitude This particular case showed an eyeground where every part of the retina of the posterior half of the eye was completely covered with heavy haemorrhages The optic disc was recognizable The mean of the b wave of the unsuccessful cases was much below that of normal cases and that of successful cases The difference was statistically significant at the 1 ‰ level The mean of the B wave also was significantly lower than those of normal (at the 1 % level) and successful (at the 5 % level) cases In Figs 12–14 the mean amplitude of the different potentials of normal successful and unsuccessful cases are plotted against light intensity Note that the b wave of unsuccessful cases turns negative" at higher light intensities (see Figs 9 and 11) In the unsuccessful cases the retinal circulation time was drastically prolonged as compared to normal and successful cases In the material presented the correlation of b and B wave amplitude and retinal circulation time was obvious When as an expression of a more severe degree of obstruction of the central retinal vessels the circulation time was prolonged beyond a certain limit the b and the B waves of the ERG were greatly reduced as a sign of marked damage of retinal function Except for one single case (see under Discussion) the a wave was not significantly changed

The mean visual acuity of the successful cases increased from 0 15 to 0 70 (range 0 5–1 0) during a mean observation time of three months For the un





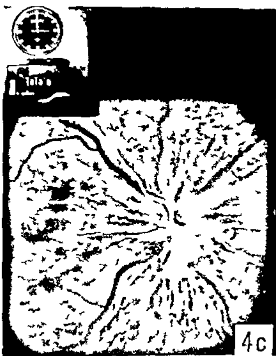
Figs 4 & 5

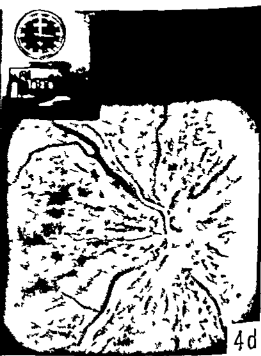
Angiogram and ERG from a patient with a thrombosis of the central retinal vein of the right eye Retinal circulation time (14 to 18 5 sec) 4 5 sec The a and b waves of the ERG are within the normal range Visual acuity at onset 0 2 three months later 0 8 Successful case

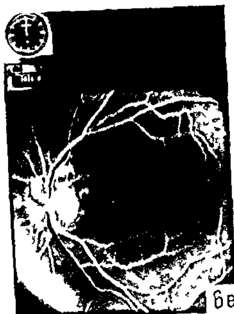
successful cases the visual acuity after a mean observation time of three months remained low ranging from amaurosis to 0 1 It is obvious that we are dealing with reversible partly reversible and irreversible damages of the retina (All

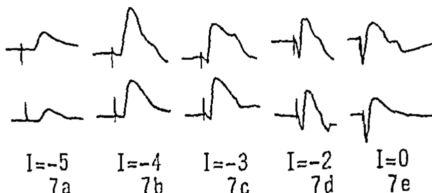

4a


4b


4c


4d





Figs 6 & 7

Angiogram and ERG from a patient with a m nor obstruction of the central retinal artery of the left eye Retinal circulation time 4 5 sec Maximum b wave less than in healthy fellow eye but not subnormal Normal a wave Visual acuity at onset perception of light Two weeks later 0 5 Successful case

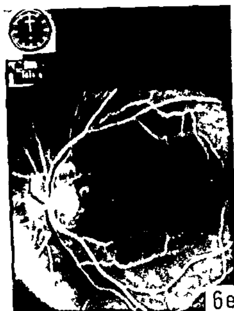
patients of the successful cases received antiocoagulants (AP®) Of the unsuccessful cases three were treated with anticoagulants and two with vasodilators only)

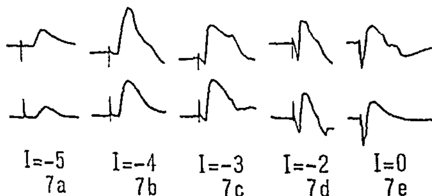

6a

6b

6c

6d





Figs 6 & 7

Ang ogram and ERG from a patient with a minor obstruction of the central retinal artery of the left eye Retinal circulation time 4 5 sec Maximum b wave less than in healthy fellow eye but not subnormal Normal a wave Visual acuity at onset percep t on of light Two weeks later 0.5 Successful case

patients of the successful cases received antiocoagulants (AP®) Of the unsuc cessful cases three were treated with anticoagulants and two with vasodilators only)

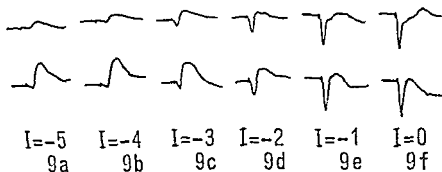

8a


8b


8c

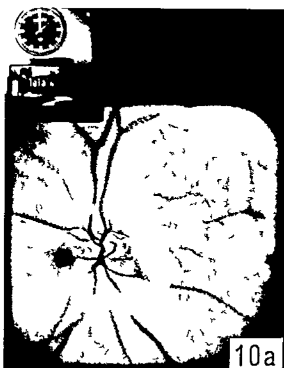

8d

8e 8f



Figs 8 & 9

Angiogram and ERG from a patient with a thrombosis of the central retinal vein of the right eye. Retinal circulation time 8.5 sec. (In the pictures shown the circulation time seems to be 9.5 sec. However checking the negatives a faint laminar flow, difficult to reproduce in a print, was seen in one of the main vein branches already at 24 sec after the injection.) Subnormal ERG with greatly reduced b wave and an a wave within normal range. At the highest intensities the b wave of the right eye turns negative. Visual acuity at onset 1/10. Same function 2.5 weeks later. Unsuccessful case.

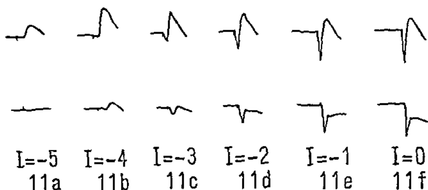

10a


10b


10c


10d





Figs 10 & 11

Angiogram and ERG of a patient suffering from a severe obstruction of the central retinal artery of the left eye Retinal c rculation time 330 sec (In the last picture a fa nt fluorescence can be seen in the peripheral parts of the lower vein branches) ERG markedly subnormal The b wave turns negative from log rel intensity -? and up Visual acuity at onset 4 60 Three days later amaurosis Ten months later still amaurosis Unsuccessful case

Table III

Cases of CVO and CAO with b potential below normal range and with a difference from the fellow eye exceeding 25 %
= unsuccessful cases

	ERG						Arm to retina time sec	Retinal circulation time sec
	a		b		B			
	mV	Diff %	mV	Diff %	mV	Diff %		
CVO ♂	0 51	− 5 6	0 12	−70 0	0 41	−24 1	24 0	8 5
CVO ♂	0 32	−40 7	0 04	−90 7	0 24	−69 2	21 0	7 0
CAO ♀	0 61	± 0	0 24	−57 9	0 62	−35 4	16 0	33 0
CAO ♂	0 48	− 4 0	0 14	−68 2	0 26	−61 2	37 0	330 circ
CAO ♂	0 44	+ 4 8	0 06	−82 4	0 25	−58 3	24 0	34 0
Mean ± S E	0 47 ± 0 05		0 12 ± 0 04		0 36 ± 0 07		24 4 ± 12 5	92 ± 62 circ

As was mentioned in the introduction the alterations of the routine ERG (Karpe (16 17)) in obstruction of the central retinal vessels are well known as are the prognostical conclusions that can be drawn from such an information (Karpe (16) Henkes (13 14) Nilsson Rendahl & Stromberg (20) Jacobson (15) Straub (28) and Karpe & Germanis (19))

The use of higher light intensities in clinical ERG (8 9 10 24 26 27) provides more information about the a wave which is of interest when studying damage at different levels of the retina With this technique in a large material of central retinal vessel obstruction Ponte (25) found that the characteristic alteration was a reduction of the b wave while the a wave was normal or supernormal However cases where the a and the b wave were both normal both decreased or both increased were also observed In smaller materials Schmöger (26) and Svěrak and collaborators (30 31 32) demonstrated reduction of both a and b waves Thus according to Ponte the same types of ERG that are seen in routine ERG are also seen after high intensity stimuli In the present investigation the successful cases all showed a normal ERG as compared to that of the fellow eye Of the unseccessful cases four were negative – (reduced b wave and normal a wave) and one was subnormal (reduced a and b waves)

The fact that the a wave in the majority of the cases is not reduced (13 14 19 25) is in good agreement with animal experimental work as to the origin of the different potentials of the ERG The blood supply of the receptor cells is coming mainly from the choroidal side (Fig 1) If the retinal circulation is reduced exclusively the receptor cells should be able to behave in a normal way whereas the remaining part of the retina would be damaged There is much evidence that the a wave is derived from a negative receptor potential (the late receptor potential) corresponding to the P III wave described by Granit (11) Brown & Wiesel (7) and Arden & Brown (1) have suggested on the basis of studies with microelectrode technique that the a wave is being generated in the visual cells Brown & collaborators (4–6) have demonstrated that clamping off the retinal circulation while reducing or abolishing other components more or less isolates a negative component considered to be a receptor potential This negative wave increased mainly because the positive b wave was abolished Nilsson & Crescitelli (21 22) showed correlating electron microscopy and electroretinography that during one particular stage of tadpole retinal development the receptor potential could be isolated This was when the receptor outer and inner segments were morphologically mature but when the synaptic structures at the receptor terminals were still lacking or immature At this stage a slow purely negative potential was obtained With the maturation of the synaptic structures allowing the excitation to be propagated farther into the *retina* a positive wave appeared An initial negativity (the a wave) remained of the

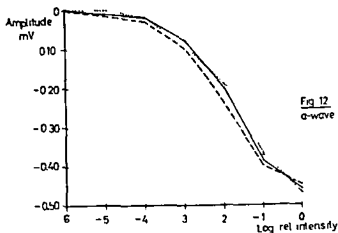


Fig 12
a-wave

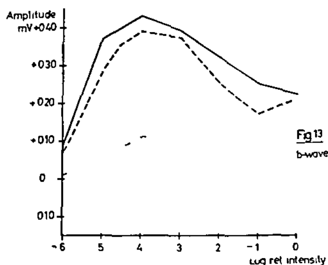


Fig 13
b-wave

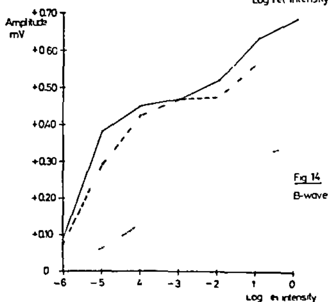


Fig 14
B-wave

——— Mean of 26 normal eyes
- - - - - — — 5 successful cases
— — 5 unsuccessful cases

original slow negative potential The positive wave is the b wave Thus it seems certain that the a wave is being generated in the receptor cells and that the b wave originates in neurons located farther vitreally presumably in the bipolar cells As a consequence taking advantage of information obtained in experimental work on animals for the understanding of clinical findings the general appearance of the ERG in central retinal vessel obstruction should include a normal or increased a wave and a decreased b wave In a larger material this is true for the majority of the cases A minor damage could leave the ERG intact or could also give rise to a hyperexcitability a supernormal ERG One likely explanation of the reduced a wave sometimes found would be the fact that haemorrhages and/or oedema accompanying retinal vascular obstruction could spread to the receptor layer causing damage in turn

The primary injury to the retina is caused by hypoxia regardless of the site of vascular obstruction Distinguishing between severe and minor reduction in blood flow is more important than distinguishing between arterial and venous obstruction However the blood flow is generally more reduced in artery than in vein obstruction Since the circulation is very seldom completely inhibited (33) the word obstruction is used rather than occlusion

In the present investigation a reduced b wave was correlated to a greatly increased retinal circulation time The shortest circulation time among the unsuccessful cases was seven seconds which is more than twice the longest circulation time among the normal cases In three of the cases the circulation time was 11–110 times the longest normal time Prior to the investigation it was not at all clear whether such a correlation existed One could consider the possibility of a severe obstruction of short duration causing the damage It now seems certain that in the majority of the cases it is a question of somewhat longer duration However in order to obtain a meaningful correlation of ERG and circulation time the examination must be done rather soon after the onset of the disease (One patient who suffered a severe thrombosis of the central retinal vein and who was treated with vasodilators only showed upon reexamination three months later a normal retinal circulation time while the ERG of the damaged retina was still markedly subnormal) The successful cases although showing a normal ERG were significantly different from the normal cases as to retinal

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Figs 10–14

Plotting of mean a wave b wave and B wave respectively against log rel intensity for normal eyes successful cases and unsuccessful cases No difference in a wave between the groups For unsuccessful cases significantly reduced b and B waves

circulation time The difference was much less than for the unsuccessful cases, though No doubt in a larger material one would find a group of cases in be tween the two groups described here They would have a moderately reduced b wave and probably a moderately prolonged retinal circulation time.

It appears that in connection with retinal vascular obstruction we are dealing with reversible and irreversible damage It is believed that newer ways to induce endogenic fibrinolysis will be of help in repairing reversible injury in a group of cases that will not heal otherwise The preliminary results are promising (2 3) ERG and fluorescein angiography together would provide the basis neces sary for selecting cases suitable for treatment *i e* cases with reversible damage.

Summary

Based on a normal material of 26 healthy eyes six cases of central retinal vein obstruction and four cases of central retinal artery obstruction were examined with fluorescein angiography and electroretinography within a week after the onset of symptoms

Using an electronic flash lamp and neutral filters the ERG was recorded with light intensities from just above threshold for the scotopic b wave to six log units above threshold 26 normal eyes were subjected to the same examination As to the ERG the pathological changes could be divided into two groups Suc cessful cases showing normal a and b waves and unsuccessful cases showing a markedly reduced b wave and a normal a wave (negative– ERG) or in one case a reduced a wave as well (subnormal ERG) The mean retinal circulation *time was for normal eyes 2 2 seconds and for successful cases 4 2* seconds with a statistically significant difference between the groups Apparently in these cases the obstruction was not severe enough to cause a serious damage to the retina The retinal circulation time for the unsuccessful cases was drastically longer ranging from 7 to 330 seconds Thus there was an obvious correlation between markedly reduced b wave amplitude as a sign of severe functional damage and greatly prolonged retinal circulation time as an expression of a pro nounced degree of obstruction The decrease in visual acuity was to a great extent reversible in the former cases whereas for the latter ones the function remained very low

The results are discussed in relation to experimental work as to the origin of the different potentials of the ERG and in relation to new and promising prin ciples in treating central retinal vein thrombosis with agents inducing endogenic fibrinolysis It seems that ERG and angiography together will provide a basis for selecting patients with reversible damage for such therapy

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From the Department of Ophthalmology Esbjerg Denmark
(Head S E Lorent en M D)

TRAUMATIC BITEMPORAL HEMIANOPSIA

Survey of the Literature and Report of a Case

BY

A BRUUN LAURSEN

In 1884 *Tuffier* and *Schoeler* & *Uhthoff* each described a case of bitemporal *hemianopsia following a skull injury* This is a *visual field defect attributed* to a median lesion of the chiasm Various reports have since been published in the literature dealing with this state with or without associated diabetes insipidus following severe skull injuries

The *bitemporal hemianopsias reported* were *incomplete or complete* in some cases with overlapping to the nasal visual fields The hemianopsias have been described as presenting in some instances sparing and in others splitting of the macula

In 1938 the Danish ophthalmologist *Osterberg* published two cases and subjected chiasms obtained post mortem to tensile tests A Danish case published by *Fledelius* (1934) might according to the author just as well be due to a tumour as to an injury This case has therefore not been included in the review of the literature given below

First a case of traumatic bitemporal hemianopsia seen by the author is reported

Case Report

The patient a girl aged 13 was on Jan 15 1968 during a strong gale hit by a falling roof She has no recollection of where the roof hit her On admission the patient was

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somnolent but fairly well oriented There was nasal liquorrhoea and a large contused wound in the middle of the forehead Both eyes were closed owing to palpebral haematomas X ray of the skull revealed fracture of the right frontal bone and comminuted fracture of both anterior fossae Right carotid arteriography showed an air bubble at the dorsum sellae Craniotomy revealed impression of the lateral part of the supraorbital margin, displacement of the glabella, crushed orbital roofs and dural lesions extending symmetrically backwards one on either side of the median plane The electroencephalogram was highly abnormal with 1 3 Hertz activity most pronounced over the right frontotemporal region Clinico neurological examination showed normal conditions The patient developed diabetes insipidus (urine volume ≥ 1900–2800 ml/24 hours) decreasing after several months Diplopia occurred which persisted for 2 or 3 months

Ophthalmological Examination

Jan 2? 1968 Right eye vision finger counting at 25 cm left eye vision 6/24 Normal position and motility Bitemporal hemianopsia was suspected on testing of visual field for finger Ophthalmoscopy showed normal optic discs and normal vessels

Jan ?6 1968 beginning optic disc atrophy of left eye

Dec 18 1969 Right eye vision 6 6 + 1 0 cyl -90° left eye vision 6/60 with no improvement by glasses 5–10 exotropia and about 3° hypertropia of left eye Both optic discs were found to be diffusely atrophic the right one predominantly so temporally Goldmann s perimeter (I/4 and V/4) revealed complete bitemporal hemianopsia with bilateral macular splitting (see figure) The cranial nerves were otherwise intact

Control on May 1 1970 includ ng ophthalmoscopy and perimetry showed unaltered conditions since Dec 18 1969

Survey of the literature and discussion

A traumatic chiasmal syndrome is rare A total of 89 cases of traumatic bitemporal hemianopsia have been found in the literature of which 81 were avail

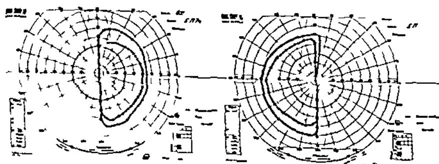


Fig
Traumatic bitemporal hemianopsia in a girl aged 13

able in their original descriptions The pathogenesis of the syndrome will be discussed below on the basis of these reports

Another 6 reports on traumatic bitemporal hemianopsia have been traced in literature These being however not available in original descriptions nor in the form of satisfactory quotations they have not been included in the present review

Cases with unilateral temporal hemianopsia and contralateral blindness were not included in the review of the literature given below because in such cases there is often found complete disconnection of one optic nerve outside the optic chiasm

Past history A common feature of the 89 cases reviewed was that all the patients had been exposed to skull injuries in the frontal or – more rarely – the temporal or parietal region Occipital injuries were recorded in few cases only In the great majority of the cases the injury was followed by loss of consciousness lasting from from few hours to 3 weeks

Skull fracture was nearly always present (in 67 out of 71 cases where this was mentioned) The observations recorded were frontal (49 cases) frontoparietal (6) frontotemporal (1) and/or basal fracture (30 cases of which 4 of the sella turcica) possibly combined with fracture of the orbital wall or the orbital roof (16 cases)

Age The age was given for 66 patients 39 ranged in age from 10 to 30 24 from 31 to 50, while 3 were over 50 years of age

Vision Good to useful vision of the best eye was most often present in the cases where information on this was available (see table) In most cases the same was true of the most affected eye but in many others pronounced visual impairment of this eye was recorded A very poor visual acuity of both eyes was infrequent Some patients had initial blindness of one or both eyes The vision then returned and the hemianopsia could be disclosed (*Liebrecht* 1912 *Paillas et al* 1959)

The visual field defects were classifiable in the following groups on the basis of the first recorded visual field for white Transitory temporal islets" of preserved visual field were not considered however

1 Complete bitemporal hemianopsia with overlapping of the defects to the nasal fields of both eyes — 5 cases
2 Complete bitemporal hemianopsia and overlapping of the defect to the nasal field of one eye — 7 cases
3 Complete bitemporal hemianopsia — 53 cases
4 Complete temporal hemianopsia and overlapping of the defect to the nasal field of one eye combined with incomplete temporal hemianopsia of the other eye — 2 cases
5 Complete temporal hemianopsia of one eye and incomplete temporal hemianopsia of the other eye — 10 cases

Table

Latest visual acuity measured for 74 patients with traumatic bitemporal hemianopsia (reports from the literature) In another 3 patients the vision is stated to have been good or normal while in 1? cases no information is given on this

Most affected eye	Best eye			
	6 6	6 9–6/1?	6/18–6/24	6/36–1/100
6 6	15	0	0	0
6 9–6/12	7	9	0	0
6/18–6 24	3	6	2	0
6 36–1/100	10	11	6	5

6 Incomplete temporal hemianopsia of both eyes 9 cases
7 Grouping impossible 3 cases

Thus complete bitemporal hemianopsia was found in 53 of the 89 reviewed cases Macular sparing and macular splitting were described almost equally often in relation to complete temporal hemianopsia in 49 and 57 eyes respectively while central scotoma in connection with this visual field defect was found in 6 eyes Macular sparing was the rule in incomplete temporal hemianopsia (21 out of 24 eyes Macular splitting was present in 3 eyes) Macular splitting or central scotoma was seen in cases with overlapping of the defect to the nasal field (9 and 10 respectively of 19 eyes)

The visual field defects were most often symmetrical though with many exceptions The defects were stationary in the majority of the cases (63 eyes with information on this) Improvement of the visual field was recorded for 17 eyes This occurred spontaneously in 9 eyes (*Jess* 1912 *Behr* 1917 and *Campbell & White 1938* among others) In the remaining cases the improvement set in after surgical removal of a haematoma adhesions or a pneumatocele together with adhesions *Calmettes & al* (1954) noticed improvement of the visual field in a patient after removal of an intrasellar haematoma but the visual field gradually became narrowed again *Hooper* (1951) and *Walsh & Hoyt* (1969) saw improvement of the visual fields after detachment of adhesions round the chiasm and *Gros & Ca alan* found extension after removal of a pneumatocele together with adhesions Increasing loss of visual field was observed in altogether 18 eyes by *Peretti* (189?) *Osterberg* (1938) *Campbell & White* 1938) *Zint* (19?5) *Hughes* (196?) *Kramer & Martens* (196?) and *Anderson & Lloyd* (1964) among others The alterations were recorded within 2 years after the injury where information on this was given

Nystagmus was recorded in 3 cases of which 1 was of the see saw type (*Fisher et al* 1968)

Operative and post-mortem findings were rarely described 2 patients presented normal chiasmas (*Pallas et al* 1959 *Logan & Gordon* 1967) and in one patient operation revealed a markedly swollen and disingrated chiasm (*Anderson & Lloyd* 1964) Other operative findings have been described above In 3 cases authopsy revealed sagittally split chiasms These have not been included in this report because the visual fields had not been tested (*Korber* 1889 *Liebrecht* 1912 *Walsh McMeel & Neetens* 1960)

Diabetes insipidus was a frequent concomitant phenomenon It was present in 26 of the 50 cases in which information on this was given This symptom used to subside within a few months

Appearance of the optic disc 3 patients presented unilateral isolated nasal pallor of the disc and 1 patient had nasal pallor of both discs Isolated temporal optic disc atrophy was noted for 8 eyes This was a unilateral phenomenon in 2 cases Diffuse or not further characterized fading of the disc was found in 87 eyes while 27 eyes had normal discs in 7 of which unilaterally

Other cranial nerve lesions Traumatic bitemporal hemianopsia was often associated with lesion of other cranial nerves Thus partial or total anosmia was present in 29 patients third cranial nerve palsy in 16 fourth nerve lesion in 1 fifth nerve lesion in 5 sixth nerve palsy in 13 seventh nerve palsy in 2 and lesion of the stato acoustic nerve in 5 patients Exotropia without associated palsy was found in 12 patients

Pathogenesis of Chiasmal Lesions The following views have been advanced concerning the mechanism of the chiasmal damage

I Primary Immediately Arisen Defects

1 Antero posterior rupture of crosssing fibres in the median plane due to momentary skull deformation with a consequent increase of the transverse diameter increased distance between the optic foramina and traction via the optic nerves at the anterior chiasmal corners Such split chiasmas have as stated been found by *Korber* 1889 *Liebrecht* 1912 and *Walsh McMeel & Neetens* (1960) in post mortem preparations

Coppez (1929) demonstrated this lesion in experiments on dead bodies with splitting and 2–3 cm separation of the frontal bones in the median plane *Osterberg* (1938) brought about grossly and microscopically visible ruptures by traction at the chiasms (post mortem preparations) In his opinion the results of these experiments correlated to the patients young ages and consequent good elasticity of the cranial bones argue in favour of the stated pathogenic hypothesis

2 Rupture or thrombosing of the fine vessels to the chiasm (*Traquair et al* 1935)

the capillary network to the median chiasmal regions being supposed to be particularly vulnerable and sparse

Another possibility is that of rupture of *François* chiasmal artery which is a branch from the anterior communicating artery to the median region of the chiasm This artery is alledgedly present in every third human being (*François Neetens & Colette* 1956)

3 Immediate contusion necrosis in the median plane (*Walsh* 1966)

4 Spiking of crossing chiasmal fibres on a bone fragment (*Campbell & White* 1938)

II Secondary Defects

1 Intrasellar haematoma (*Calmettes et al* 1954)

2 Pressure from pneumatocele (*Gros & Cazaban* 1951)

3 Perichiasmal arachnoiditis with adhensions (*Gros & Cazaban* 1951 *Paillas et al* 1959 *Walsh & Hoyt* 1969)

4 Pressure from callus formation (*Jess* 1912)

Any one of the pathogenic possibilities stated in the literature may perhaps be met with though at varying frequencies However the damage seen in relation to intrasellar haematoma arachnoiditis pneumatocele and callus formation is probably due to an obstructed blood supply as the defects developed slowly in these cases *Gros & Cazaban* (1951) showed a central excavation dorsally on the chiasm in a patient with pneumatocele

An antero posterior rupture possibly takes place in cases of macular splitting In cases of macular sparing on the other hand it is difficult to explain why all crossing fibres should burst except the macular which latter according to *Ronne* (1910) cross postero dorsally in the chiasm Macular sparing may not really exist but may be an artefact due to unsteady fixation as claimed by *Danis* (1954) who has published the most comprehensive literary review on traumatic bitemporal hemianopsia Provided the macular sparing is real the hemianopsia can best be explained by a vascular disorder in these cases and not by direct rupture of crossing fibres because according to *Hughes* (1958) the macular fibres at their site of crossing in the chiasm are supplied by the superior hypophyseal artery or a branch of the posterior communicating artery In cases of traumatic bitemporal hemianopsia with macular sparing these arterial branches might remain undamaged while the chiasmal artery and the branches from Dawson s arcade supplying the remaining crossing fibres in the median plane become injured On the other hand in monkeys *Hoyt & Luis* (1963) found crossing of the macular fibres almost anywhere in the chiasm mingled with the other crossing fibres If this finding can be transferred to man, an explanation of the macular sparing on a purely vascular basis will be difficult.

Dependent on the severity of the lesion loss is seen first of the upper tempo

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Further references may be obtained on application to the author

From the Helsinki University Eye Hospital
(Head Prof Salme Vannas M D
Helsinki Finland

IRIDENCLEISIS

Results of 124 consecutive operations for chronic open angle glaucoma in 1964–1968

BY

AHTI TARKKANEN and LARS-ERIK ESKELIN

The purpose of this study was to assess the results of iridencleisis operations done for chronic open angle glaucoma at the Helsinki University Eye Hospital during the five year period 1964–1968 Iridencleisis has been the standard drainage operation in this teaching hospital because of the simplicity and the fact that the anterior chamber is less likely to remain flat postoperatively (*Becker & Shaffer 1965*) An attempt was made to correlate the results with regard to the patients age and presence of pseudoexfoliation of the lens capsule Furthermore as about one half of the operations were performed by the residents in training it was decided to study this matter also In assessing the results attention was paid to the control of the ocular tension and possible deterioration of the visual acuity postoperatively

Material and Methods

A very conservative attitude has been prevalent in the management of chronic open angle glaucoma at our hospital as would appear from the total number of

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failure rate and the number of eyes with visual deterioration were slightly higher in the capsular form indicating the difficulties in obtaining good drainage in this form of glaucoma Similarly of the 13 eyes with persistent hypotension 9 belonged to the chronic simple group and only 4 in the capsular glaucoma (Table 4) In none of these however had macular edema or disfiguring astigmatism appeared Approximately one half of the operations were performed by the consultants and the other half by the residents in training (Table 5) Although the more difficult cases were primarily handled by the consultants the tensions were controlled in 92 per cent in their series compared to the 86 per cent in the cases operated by the residents On the contrary the number of eyes with visual deterioration was higher among the consultants cases

Eight eyes were reoperated varying from 9 days to 14 months from the primary operation with the resultant control of the tension in every case (Table 6) Simple revision of the primary iridencleisis wound was performed in five eyes cyclodialysis in two and posterior sclerotomy with air injection in one case *Three of the eyes showed visual deterioration following the reoperation* and in all those cases revision had been performed It is of interest however that

Table 4

Persistent hypotension and clinical form of chronic open angle glaucoma

Type of glaucoma	Number of eyes	Number of eyes with hypotension	Per cent
Chronic simple	70	9	13
Capsular	54	4	7

Table 5

Failure rate visual deterioration and type of surgeon

Type of surgeon	Number of eyes	Number of failures	Per cent	Number of eyes with visual deterioration	Per cent
Consultant	61	5	8	17	28
Resident	63	9	14	11	17

Table 6
Reoperations

Clinical type of glauc ma	Type of reoperation	Time interval from the primary operation	Result	Visual deterioration
Capsulare	Revision	8 months	Normalization	None
Capsulare	Revision	2 weeks	Normalization	Yes
Capsulare	Revision	2 months	Normalization	Yes
Capsulare	Cyclodialysis	9 months	Normalization	None
Capsulare	Revision	1 month	Normalization	None
Chronic simple	Posterior sclerotomy	9 days	Normalization	None
Chronic simple	Cyclodialysis	14 months	Normalization	None
Chronic simple	Revision	4 months	Normalization	Yes

in all cases the outcome of reoperation was good regardless of the type of re operation

Discussion

Some recent reports indicate that the tension has been controlled in 60 to 90 per cent of eyes with chronic open angle glaucoma following iridencleisis (*Becker & Shaffer* 1965 *Boles Carenini & Rivara* 1963 *Gjessing* 1970 *Haisten & Guyton* 1959 *Leydhecker* 1966 *Kutschera & Ebner* 1965 *Scheie* 1962) It is of special interest that in the series reported by Leydhecker 70 per cent were controlled after one year and 90 per cent after six to nine years postoperatively This is in agreement with the observation of *Sugar* (1960) that two thirds of successful blebs changed and in most of these there was an increase in bleb size during the period of observation In these terms it is to be expected that in our series the operative failures have already been discovered and the success rate of 89 per cent may be regarded as characteristic to this series

Visual deterioration of at least two lines occurred in 23 per cent of our cases This figure is comparable with the report of *Kutschera & Ebner* (1965) who noticed that the visual acuity remained unchanged following iridencleisis in 63 per cent of the eyes In the careful study of *Haisten & Guyton* (1959) cataract formation or progression was seen in 33 per cent after iridencleisis Hypotony did not seem to be the reason for cataract formation as has also been described by *Leydhecker* (1966) Similarly the visual deterioration was the feature of both the chronic simple glaucoma and the capsular glaucoma eyes (Table 4) The cataract formation may be regarded solely as an operative complication as pseudoexfoliation is not associated with increased cataract formation (*Tarkkanen* 1962) In a survey of 83 successfully filtering eyes with chronic open angle glaucoma 38 per cent were found to have developed cataracts (*Sugar* 1970) and it was concluded that the operations can cause potentiate or accelerate the metabolic disturbances leading to cataract formation The average period from the time of the filtering operation to the cataract extraction was almost six years (*Laatikainen* 1970)

Although the more difficult cases were operated by the consultants the tensions were controlled more frequently as compared to the cases handled by the residents (Table 5) There seems to be general agreement that a minimum of manipulation of the iris is most essential in obtaining a successful result (*Haisten & Guyton* 1959) In these terms good surgical experience may be more important It would seem justified to require practice of iridencleisis with animal eyes in similar fashion as is done before cataract surgery at our hospital (*Tarkkanen & Eskelin* 1968)

Of the 14 cases of failures 8 were reoperated with good results (Table 6) This would increase the success rate from 89 to 95 per cent Unfortunately visual deterioration took place in three of the eight eyes increasing the percentage of visual deterioration to 27 per cent In these terms both new more effective medical means as well as less traumatic methods of operation like partial trabeculectomy are to be welcomed in the management of chronic open angle glaucoma

Summary

During the five year period 1964–1968 124 eyes with chronic open angle glaucoma were subjected to iridencleisis A very conservative attitude in the management of open angle glaucoma is revealed by the fact that during the same period 3150 intraocular operations and a total of 10 114 ophthalmic operations were performed The criteria of the control of the ocular tension hypotony and visual deterioration have been presented The tensions were controlled in 89 per cent and visual deterioration took place in 23 per cent Persistent hypotony developed in 10 per cent The data have been further analyzed with regard to the patient s age the presence of pseudoexfoliation and the type of surgeon whether a consultant or a resident in training Eight eyes with initial failure were reoperated with successful control in all but visual deterioration in three cases

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Reprint requests to
Helsinki University Eye Hospital
Haartmaninkatu 4 Helsinki 29 Finland (Dr Tarkkanen)

From the Ophthalmic Department of the University Hospital Turku Finland
(Head Prof Arvo Oksala)

EXPERIMENTAL OBSERVATIONS ON THE ACOUSTIC SHADOW IN B SCAN EXAMINATION OF THE EYE

BY

ARVO OKSALA & SIRKKA LIISA JÄÄSLAHTI

Experimental and clinical observations have shown that in the ultrasonic diagnosis of the eye and the orbit a relative or absolute acoustic shadow appears quite often As the lens strongly attenuates ultrasound i e 20 db more than the vitreous it causes a strong relative shadow Thin parts of the eye such as the cornea and sclera produce a slight acoustic shadow if the examination is carried out at right angles against them The acoustic shadow caused by the aqueous humor and the vitreous is in practice insignificant If the ultrasound hits the cornea and sclera at approx 30 angle the attenuation of ultrasound rises and when the angle of incidence increases to 70° an absolute acoustic shadow comes into being because of total reflection (*Oksala & Hakkinen* 1969 a) Any tissues of the eye and orbit may produce an acoustic shadow if the angle of incidence reaches a certain point i e approx 40 (*Oksala & Hakkinen* 1969 b)

Very few experimental and clinical studies have been made on the attenuating effect of various tissues and the acoustic shadow caused by it *In addition* to the persons mentioned above *Vanysek & Preisova* (1965) have shown that an intra ocular tumor lowers the rear eye wall echo behind the tumor *Nover & Glanschneider* (1965) were able to show that both the lens and a melanoma attenuate ultrasound equally *much* Due to the method itself and its smaller sensitivity an acoustic shadow appears *more* often in B scan where its significance from the point of view of diagnosis is greater than in A scan Therefore this paper is

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based on experimental B scan studies of the appearance of a relative and absolute acoustic shadow under certain circumstances

Material equipment and method of research

Acoustic shadows were produced in whole pig eyes from newly slaughtered animals When the effect of the optic nerve was examined we used a rear wall calotte of the sclera with a 1 cm long optic nerve The tissues in the echograms of which the acoustic shadows could be seen were 7 different carcinoma uteri tissues 2 different myoma uteri tissues and copper wire as a foreign body The acoustic shadow was also observable in the echoes of the bottom of the bowl that was used at the examination

The examination were made by Kretztechnik s ultrasound equipment Model 7100 MA which projects simultaneously both A- and B scan pictures The transducer of 8 MHz/5 mm was slightly focused and the focused area lay at a distance of approx 30 mm from the transducer With the amplification that was used the diameter of this area was about 2 mm The movement of the transducer was linear and the distance between the acoustic cross sections 2 mm

The examinations were carried out in a bowl of water in which the transducer was immersed An eye or a rear wall calotte was placed in the water on a stand made of very thin copper wire A piece of the tumor tissue that was being examined or the copper wire denoting a foreign body was placed under the eye The distance between the transducer and the surface of the eye was 5 mm and that between the eye and the tumor tissue 10 mm The diameter of the tumor tissue was 10 mm the length of the copper wire 20 mm and its diameter 2 mm When the rear wall calotte was used to examine the acoustic shadow produced by the optic nerve the distances and sizes remained the same

Relative and absolute acoustic shadows were searched for by the following methods First the sound beam moved through the lens via the center of the eye and the cornea which produced the attenuating effect of the lens at its highest Then several acoustic cross sections at a distance of 2 mm from one another were made through the sclera but past the lens At the latter examinations the eye was placed on the stand so that either the cornea or the equator of the eye lay on top When the acoustic shadow caused by the optic nerve was examined the position of the rear wall calotte was changed so that the angle of incidence from the sound beam in respect to the optic nerve varied a lot

At the examination of the acoustic shadow caused by a whole eye on tumor tissue photos were taken of 160 echograms When the effect of the whole eye on the B scan picture of a foreign body was examined 40 echograms were photographed and equally many of the effect of the optic nerve

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Results

The results were coherent and easily repeatable under all examinations conditions and therefore they will be presented in the form of some photographs only

The attenuation of ultrasound and the acoustic shadow caused by the lens and the sclera

Fig 1 shows A and B echograms of carcinoma uteri In Fig 1 A one can see the echoes obtained by A scan on the left the echo reflected by the copper wire on the right the echoes from the bottom of the bowl and in the middle the echogram of the tumor tissue Fig 1 B presents a B scan echogram On top we have the linear echo of the copper wire stand while the lowest echoes come from the bottom of the bowl In the middle one can see echoes reflected by the tumor tissue (T) They show clearly that B scan produces echoes only from the anterior part of the tumor while the deeper parts of it are acoustically homogeneous These pictures also prove that the sensitivity of A scan is better because the same amount of amplification in A scan presents the whole tumor as acoustically heterogeneous Fig 1 B shows that even a 1 cm thick tumor tissue produces a weak relative acoustic shadow in the echoes of the bottom of the bowl

Fig 2 represents the effect of the whole eye on the echogram of a tumor tissue under two different circumstances i e 1) when the sound travels through the lens (Fig 2 A) and 2) when the sound travels through the eye but past the lens (Fig 2 B) In the former case a strong relative acoustic shadow appeared in the echograms of the tumor tissue and the bottom of the bowl In Fig 2 A the tumor tissue reflects no echoes and the part of the bottom of the bowl which

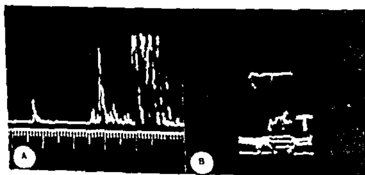


Fig 1
The echograms of carcinoma uteri Fig 1 A was obtained by A scan and 1 B by B scan.

based on experimental B scan studies of the appearance of a relative and absolute acoustic shadow under certain circumstances

Material equipment and method of research

Acoustic shadows were produced in whole pig eyes from newly slaughtered animals When the effect of the optic nerve was examined we used a rear wall calotte of the sclera with a 1 cm long optic nerve The tissues in the echograms of which the acoustic shadows could be seen were 7 different carcinoma uteri tissues 2 different myoma uteri tissues and copper wire as a foreign body The acoustic shadow was also observable in the echoes of the bottom of the bowl that was used at the examination

The examination were made by Kretztechnik s ultrasound equipment, Model 7100 MA which projects simultaneously both A and B scan pictures The transducer of 8 MHz/5 mm was slightly focused and the focused area lay at a distance of approx 30 mm from the transducer With the amplification that was used the diameter of this area was about 2 mm The movement of the transducer was linear and the distance between the acoustic cross sections 2 mm

The examinations were carried out in a bowl of water in which the transducer was immersed An eye or a rear wall calotte was placed in the water on a stand made of very thin copper wire A piece of the tumor tissue that was being examined or the copper wire denoting a foreign body was placed under the eye The distance between the transducer and the surface of the eye was 5 mm and that between the eye and the tumor tissue 10 mm The diameter of the tumor tissue was 10 mm the length of the copper wire 20 mm and its diameter 2 mm When the rear wall calotte was used to examine the acoustic shadow produced by the optic nerve the distances and sizes remained the same

Relative and absolute acoustic shadows were searched for by the following methods First the sound beam moved through the lens via the center of the eye and the cornea which produced the attenuating effect of the lens at its highest Then several acoustic cross sections at a distance of 2 mm from one another were made through the sclera but past the lens At the latter examinations the eye was placed on the stand so that either the cornea or the equator of the eye lay on top When the acoustic shadow caused by the optic nerve was examined the position of the rear wall calotte was changed so that the angle of incidence from the sound beam in respect to the optic nerve varied a lot

At the examination of the acoustic shadow caused by a whole eye on tumor tissue photos were taken of 160 echograms When the effect of the whole eye on the B scan picture of a foreign body was examined 40 echograms were photographed and equally many of the effect of the optic nerve

Results

The results were coherent and easily repeatable under all examinations conditions and therefore they will be presented in the form of some photographs only

The attenuation of ultrasound and the acoustic shadow caused by the lens and the sclera

Fig 1 shows A and B echograms of carcinoma uteri In Fig 1 A one can see the echoes obtained by A scan on the left the echo reflected by the copper wire on the right the echoes from the bottom of the bowl and in the middle the echogram of the tumor tissue Fig 1 B presents a B scan echogram On top we have the linear echo of the copper wire stand while the lowest echoes come from the bottom of the bowl In the middle one can see echoes reflected by the tumor tissue (T) They show clearly that B scan produces echoes only from the anterior part of the tumor while the deeper parts of it are acoustically homogeneous These pictures also prove that the sensitivity of A scan is better because the same amount of amplification in A scan presents the whole tumor as acoustically heterogeneous Fig 1 B shows that even a 1 cm thick tumor tissue produces a weak relative acoustic shadow in the echoes of the bottom of the bowl

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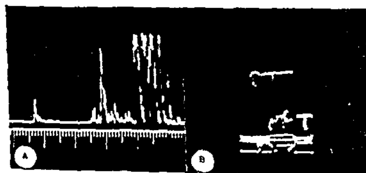


Fig 1

The echograms of carcinoma uteri Fig 1 A was obtained by A scan and 1 B by B scan.

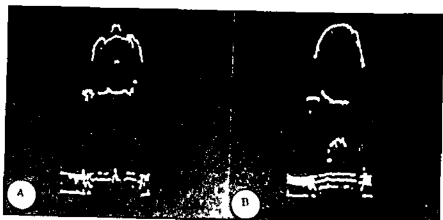


Fig 2
The effect of the whole eye on the echograms of tumor tissue and the bottom of the bowl In 2 A the sound has travelled through the whole eye and the lens while in 2 B the beam has travelled disasclerally past the lens

corresponds to the position of the eye reflects considerably fewer echoes than the same area for example in Fig 1 B In half the cases the tumor tissue reflected no echoes and in the other half some light points reflected by the tumor were obtained In Fig 2 B the sound beam traveled through the eye at the equator but past the lens In the picture one can see the echoes from the anterior and rear walls of the eye as well as the echogram of the tumor tissue The latter is somewhat smaller in size than the one obtained at an examination without the eye Furthermore Fig 2 B shows that without the effect of the lens the whole eye causes a slight relative acoustic shadow in the echograms of the tumor tissue and the bottom of the bowl

Fig 3 presents the same examination conditions as Fig 2 but in this case the investigated object was a piece of copper wire In Fig 3 A one can see the effects of the eye and the lens Fig 3 B shows the results when the examination was made through the eye parallel to the equator but past the lens At the examination through the whole eye and the lens the copper wire reflected either 1–3 separate echo peaks (in Fig 3 A two peaks are seen) or no observable echoes Fig 3 B shows that when the examination was made through the whole eye but past the lens the copper wire reflected an echogram which was real in shape Fig 3 also shows that the relative acoustic shadow caused by the whole eye and the lens in the echograms of the wire and the bottom of the bowl is distinctly stronger than the shadow at the diascleral examination

Fig 4 represents an absolute acoustic shadow produced by the surface of the eye as a result of which the tumors reflect no echoes and even the echoes from the bottom of the bowl disappear from an area that is a few millimeters wide An absolute shadow like this is caused by a total reflection of ultrasound on the

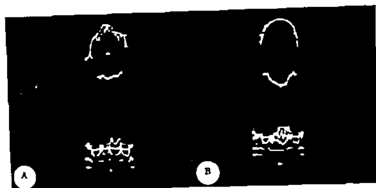


Fig 3

The effect of the whole eye on the echograms of the copper wire and the bottom of the bowl 3 A presents an examination through the lens and 3 B diasclerally past the lens



Fig 4

A total reflection on the surface of the eye produces an absolute acoustic shadow which can be seen as an approx 7 mm wide area in the echograms of the bottom of the bowl Tumor echoes cannot be seen at all

surface of the eye and it appears when the sound beam meets the surface of the eye at an approx 10° angle of incidence This kind of an angle of incidence is formed when the sound beam hits the eye near its equator while the eye is placed on the stand with the cornea on top or when the sound beam hits the eye 5–8 mm behind the equator while the eye is placed on the stand with the equatorial area on top An absolute acoustic shadow was obtained on the surface of the eye from an area which was 2 3 mm long The width of the shadow was 5 8 mm

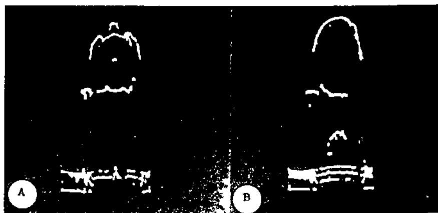


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The effect of the whole eye on the echograms of tumor tissue and the bottom of the bowl In 2 A the sound has travelled through the whole eye and the lens while in 2 B the beam has travelled diascleraly past the lens

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dow and that this shadow is much stronger if the examination is made through the lens In addition to that this investigation confirms previous experimental observations on the fact that any tissue in the eye or orbit may in the form of total reflection cause an absolute acoustic shadow if the angle of incidence reaches a certain point In previous studies a total reflection was discovered by the use of sound field measurements in A scan In this study total reflection has been verified experimentally by B scan

An absolute acoustic shadow was easily obtainable and its width was 5–8 mm The absolute shadow caused by various parts of the eye naturally extends all the way to the orbital echograms Its impeding effect on ultrasonic diagnosis is however greatly diminished by the continuous slight movements of the eye. The relative shadow produced by the lens has much more clinical significance The smaller the total sensitivity of the equipment the greater is the effect of the shadow

During the course of this investigation examinations were made side by side by both A and B scans A scan proved out to be somewhat more sensitive in all cases In clinical ultrasonic diagnosis the analysis of echograms always has to be made on the basis of A scan pictures while B scan is in many cases better suitable for the localization of pathological areas particularly in regard to the respective positions of the tissues

Summary

In an experimental B scan investigation where pig eyes were used the surface of the eye and the optic nerve were observed to cause under certain circumstances through total reflection an absolute acoustic shadow When the examination was made through the whole eye a slight relative shadow appeared If the examination was made through the lens the shadow was much stronger The disturbing effect of the absolute shadow on clinical diagnosis is diminished by the continuous movement of the eye A scan proved to be more sensitive than B scan

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The attenuation and shadow caused by the optic nerve

As it was mentioned above a scleral calotte with a 1 cm long optic nerve was used when the acoustic shadow caused by the optic nerve was examined The examination was made so that the sound beam always hit the nerve By changing the position of the calotte we were able to produce if we wanted either relative or absolute acoustic shadows caused by the optic nerve In Fig 5 A one can see an echogram reflected by myoma uteri On top one can first recognize the linear echo from the copper wire and on the bottom the echoes of the bowl The echogram of the tumor (T) is seen between them The tumor tissue produces a relative acoustic shadow in the echoes of the bottom of the bowl Fig 5 B shows an absolute acoustic shadow caused by the optic nerve which extends all the way through the tumor tissue and the bottom of the bowl with a width of a couple of millimeters On the top one can see the echoes of the rear wall calotte *When the examination was made past the optic nerve* only weak relative shadows were obtained

Discussion

The attenuation of ultrasound in a tissue is caused by several different factors such as absorption reflection refraction and scattering The attenuation of ultrasound means the appearance of a relative sometimes an absolute acoustic shadow Our investigations show that from the point of view of clinical ultrasonic diagnosis the whole eye always produces a slight relative acoustic sha

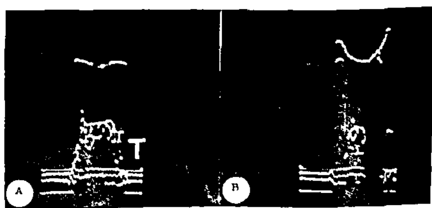


Fig 5

In 5 A one can see an echogram reflected by myoma uteri (T) and in 5 B an absolute shadow caused by the optic nerve in the echograms of the tumor tissue and the bottom of the bowl

From the Helsinki University Eye Hospital
(Head Prof Salme Vannas M D)

MODIFIED GONIOPUNCTURE IN THE TREATMENT OF CONGENITAL GLAUCOMA

BY

SALME VANNAS & S POHJOLA

When doing a goniotomy on a girl with juvenile glaucoma Scheie accidentally perforated the corneoscleral wall in the area of the trabeculum This resulted in filtration into the subconjunctival space at the site of the counterpuncture formation of an opening at the corresponding site in the chamber angle and permanently decreased intraocular pressure As a result of this mishap *Scheie* (1950) developed a surgical technique for the treatment of juvenile and congenital glaucoma and gave it the name goniopuncture

Later experience has shown that goniopuncture is a serviceable method for treatment of congenital glaucoma pressure is normalized in about half of those thus treated and there are few complications (*Scheie* 19э0 *1959 1961 Haas* 1955) In addition it should be taken into account that goniopuncture does not preclude a subsequent goniotomy in the same eye should it prove necessary On the basis of reports in the literature goniopuncture was introduced in 1965 at the Helsinki University Eye Hospital for management of congenital glaucoma Our experience with this method will be dealt with below

Material and technique

Up to the present time nine children diagnosed as having congenital glaucoma have been treated by goniopuncture in our hospital The disease was bilateral in six of these cases A total of ?3 goniopunctures have been performed in 13 eyes

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Table 1
Early cl n cal features of eyes with congenital glaucoma

Patient	Early signs	Diagnosis: Age	Diagnosis: Tension (T) mmHg	Diagnosis: Corneal diameter ⌀	Interval between early signs and diagnosis
1	Tearing probing at age of 2 weeks At *3 months* right eye of strange appearance At 6 months right cornea enlarged	*7 mo*	T = 32	⌀ = 13.5 mm	6 5 mo
2	*At birth* right cornea milky opaque and large	1 mo	T od = 70 os = 98	⌀ od = 14 0 mm os = 12 0 mm	*1 mo*
3	At birth right cornea greyish DG keratitis Treated topically with steroids At 7 months cornea enlarged and milky opaque	8 mo	T = 60	⌀ = 13 mm	*8 mo*
4	Shortly after birth both eyes large At 5 months right eye larger than left At 8 months right *cornea* cloudy and eye red	8 mo	T od = 51 os = 17	⌀ od = 14 mm os = 13 mm	*8 mo*
5	At one year of age right eye red for several *months* vernal conjunctivitis diagnosed treated 2 years with local steroids Hospitalized at 3 years for *superficial* keratitis OD	3 yrs 4 mo	T od = 45 *os* = 40	⌀ od = 12 5 mm os = 11 0 mm	about 3 yrs
6	Eyes large at birth At 2 months started *rubbing* left eye photophobia tearing	4 5 mo	T od = 45 *os* = 50	⌀ od = 13 0 mm os = 14 0 mm	4 5 mo
7	Big eyes at birth	3 5 mo	T od = 43 *os* = 59	⌀ od = 15 5 mm os = 15 0 mm	3 5 mo
8	At birth both corneas cloudy Treated *with local* steroids	1 mo	T od = 28 *os* = 28	⌀ od = 13 0 mm os = 12 0 mm	1 mo
9	At ? months right eye larger than *left*	6 mo	T od = 55 *os* = 36	⌀ od = 15 0 mm os = 12 0 mm	4 mo

In two children who each had bilateral elevation of ocular tension the pressure has decreased spontaneously in one of the eyes

Early signs and diagnosis It is generally emphasised that early recognition and early treatment are essential for good results to be obtained in congenital glaucoma Therefore it seems good to consider here first the nature of the early signs found in this series and the time taken for correct diagnosis to be reached Such an evaluation is particularly useful since it gives an idea of the kind of eyes here treated with goniopuncture (Table 1)

In seven patients the symptoms were present at or shortly after birth in two patients during the first months of life There was enlargement of one or both eyes greyness or milky colour of the cornea tearing photophobia eye redden ing and rubbing Faulty diagnosis were keratitis dacryostenosis and conjunc tivitis vernalis Despite the fact that the clinical picture clearly pointed to con genital glaucoma it took a medium time of 4 5 months to establish diagnosis

Owing to the long duration of symptoms the corneal diameter was in six eyes 14 mm or more at the time of operation In two eyes the cornea was milky white

Goniopuncture The operation is performed in general anaesthesia without a gonioscopy lens (The lens is removed after examination of the chamber angle) Before operation pilocarpine is instilled to make the pupil miotic Saline is in jected subconjunctivally into the site of the counterpuncture at the 6 o clock position beside the limbus in order that the goniopuncture knife should not per forate the conjunctiva As distinguished from the *Scheie technique* (1950 1961) a needle is then inserted nasally from above into the anterior chamber and arti fical aqueous or saline is injected through it to keep the depth of the anterior chamber unchanged during the procedure The puncture is made in the tempo ral limbus (3 or 9 o clock) the tip of the knife carried across the anterior cham ber approximately to the 6 o clock meridian where the corneoscleral wall is punctured in such a manner that the tip of the knife emerges into view sub conjunctivally The knife is turned 90 degress and back and then withdrawn There have been no complications apart from slight hyphaema at the counter puncture site in three cases At the end of the operation the pupil is enlarged with neosynephrine Instillation of pilocarpine is started the next day Follow up pressure measurements have usually been made in general anaesthesia two weeks one month three months six months and twelve months after operation

Results

The intraocular pressure was maintained at 22 mmHg or lower in nine of 13 operated eyes the period of observation varying from one year to four years and six months (Table 2)

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5	At one year of age right eye red for several months vernal conjunctivitis diagnosed treated 2 years with local steroids Hospitalized at 3 years for superficial keratitis OD	3 yrs 4 mo	T od = 45, os = 40	Φ od = 12 5 mm, os = 11 0 mm	about 3 yrs
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Table 2

Results of goniopuncture

Patient	Eye	Age at the first gonio pun ture	No of gonio punctures	Follow up period	Final tension mmHg	Papilla	Visual acuity	Results*)	Remarks
1	OS	7 mo	1	4 yrs 6 mo	22	excavated	0 2	+	
2	OD	1 mo	2	4 yrs 4 mo	40	not visible	amaurosis	—	Additional operation 2 × cyclodiathermy
	OS	8 mo	1	3 yrs 8 mo	20	excavated	0 5	+	
3	OD	8 mo	4	3 yrs 6 mo	60	not visible	amaurosis	—	
4	OD	9 mo	2	1 yr 6 mo	17	excavated	central fixation	+	
5	OD	3 yrs 4 mo	1	2 yrs 7 mo	21	excavated	0 2	+	
	OS	3 yrs 8 mo	2	2 yrs 3 mo	17	excavated	1 0	+	
6	OD	5 mo	1	2 yrs 3 mo	17	excavated	central fixation	+	
	OS	5 mo	1	2 yrs 3 mo	15	excavated	central fixation	+	
7	OD	5 mo	1	1 yr	17	excavated	central fixation	+	
	OS	5 mo	4	1 yr	40	excavated	?	—	Additional operation 2 × goniotomy
8	OD	6 mo	1	1 yr	20	not excav	central fixation	+	
	OS		-		17				OS Spontaneous nor malization of intra ocular tension
9	OD	6 mo	2	1 yr	40	excavated	?	—	Additional operation 1 goniotomy
	OS		-		19				OS Spontaneous nor malization of intra ocular tens on

*) + = T ≤ 22 mmHg

In seven eyes the first goniopuncture was successful in two eyes two gonio punctures were needed to normalize pressure in one 12 months in the other three months following the first procedure

The four unsuccessful cases included two in which *the cornea was opaque* and hazy preoperatively One of these was treated with four goniopunctures the other twice with goniopuncture and twice with cyclodiathermy without success The next two failures occurred in the poorer eye in bilateral glaucoma the diameter of the cornea being in both cases 15 mm at the time of operation One of these eyes was subjected to four goniopunctures and one goniotomy the other to two goniopunctures and one goniotomy without result

As regards visual acuity our data are still incomplete because the patients were so young Examination results are available for four eyes in which vision was 1 0 0 5 0 2 and 0 2 In the others our impression was that central fixation was present In all except one eye there was an excavated papilla On slit lamp microscopy one year after operation distinct filtration was found in no single case at the site of the counterpuncture

Discussion

Although in the case of most eyes operated on by goniopuncture there was an interval of several months between the onset of signs and the diagnosis satis factory pressure control was accomplished in nine eyes out of 13 (70 %) Despite the comparatively sharp criticism raised against goniopuncture (*Worst* 1964) the results are of the same order as those attained by goniotomy *Barkan* 80% (1955) *Bietti* 80% (1964) *Haas* 71% (1955) and *Leydhecker* 72% (1960) *Scheie* (1961) reported that he had obtained control of pressure by goniotomy in 69 % by goniopuncture in 52 % and by a combination of the two in 76 % In our series very limited it is true a corresponding result was reached by go niopuncture performed alone This may be due to the modified method used i e to the fact that a deep anterior chamber was maintained throughout the operation Thus the danger of postoperative anterior adhesions and also of postoperative bleeding is reduced

Scheie considers that if the eyes have done well for three months after ope ration recurrences are rare In one of our cases the pressure rose again after being normal for a year This tendency is clearly apparent in *Leydhecker s* go niotomy series the results were good in 80 % of the cases observed for 6–12 months but the figure dropped to 50 % after an observation period of six years Surprisingly we were not able to demonstrae definite subconjunctival filtration at the site of the counterpuncture This agrees well with an observation made by *Ferguson* (1950) he noted that if a filtrating bleb forms accidentally at go

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niotomy it invariably disappears later Thus it is possible that goniopuncture and goniotomy may have the same mechanism of action not yet definitely known *Schaffer* (1964) for instance found that a minute opening made with the tip of a knife in the surface of the trabeculum can cause a substantial increase in outflow facility

Summary

In spite of the relatively well defined clinical picture of congenital glaucoma (large eye corneal opacity tearing photophobia eye reddening and rubbing) several months mostly elapsed between the onset of signs and definitive diagnosis

Good ocular tension control was obtained by means of modified goniopuncture in nine eyes of 13 and there were no postoperative complications in these cases

In two eyes a spontaneous cure occurred

Goniopuncture can be recommended as the primary operation in the treatment of congenital glaucoma because of the slight risk of complications and the encouraging results obtained In addition it should be taken into account that goniopuncture does not preclude a subsequent goniotomy or trabeculotomy should it prove necessary

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Department of Ophthalmology University of Umeå
S-901 85 Umeå Sweden

APPLANATION TONOGRAPHY AT CONSTANT INTRAOCULAR PRESSURE

I Basic considerations

BY

ERIK LINNÉR and WILLIAM THORBURN

Summary

Errors introduced by the changing intraocular pressure during tonography are pointed out and the reasons for the advisability of a procedure of constant pressure tonography are discussed. Requirements necessary for performing applanation tonography at constant intraocular pressure are analyzed.

Key words Applanation Tonography – Constant Pressure Tonography – Intraocular Pressure – Tonography

Although tonography has been widely used for twenty years the method is still impaired by serious errors and uncertainties. The clinical usefulness of the method is therefore limited.

The changing intraocular pressure during the tonographic procedure constitutes one of the main problems. It is difficult to estimate the coefficient of ocu

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niotomy it invariably disappears later Thus it is possible that goniopuncture and goniotomy may have the same mechanism of action not yet definitely known *Schaffer* (1964) for instance found that a minute opening made with the tip of a knife in the surface of the trabeculum can cause a substantial increase in outflow facility

Summary

In spite of the relatively well defined clinical picture of congenital glaucoma (large eye corneal opacity tearing photophobia eye reddening and rubbing) several months mostly elapsed between the onset of signs and definitive diagnosis

Good ocular tension control was obtained by means of modified goniopuncture in nine eyes of 13 and there were no postoperative complications in these cases

In two eyes a spontaneous cure occurred

Goniopuncture can be recommended as the primary operation in the treatment of congenital glaucoma because of the slight risk of complications and the encouraging results obtained In addition it should be taken into account that goniopuncture does not preclude a subsequent goniotomy or trabeculotomy should it prove necessary

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Different approaches to the problem of producing a deformation of the eye ball are possible The deformation and the change in intraocular volume produced by a Schiotz tonometer is complicated and difficult to determine accurately We preferred a deformation produced by a plane surface in contact with the eyeball The first alternative is a probe made of a hard material with a plane surface which is applied to the cornea Under ideal circumstances considering the cornea as a perfectly dry thin elastic and flexible membrane the relationship between the area of applanation the intraocular pressure and the applanating force follows the Imbert Fick law The surface tension of the tear film and the bending force of the cornea are factors which cannot be neglected These two factors cancel each other out when the diameter of the applanated area is 3 06 mm and this area was chosen in the method of applanation tonometry by Goldmann At larger areas of applanation the bending forces of the cornea and the surface tension might not be equal However investigations by Gloster and Perkins (1) and Linnér (3) showed that Imbert Fick s law can be applied even at larger areas of applanation

According to Imbert Fick s law it is necessary to determine directly two of the factors The force is the easiest to measure and the area of applanation the most difficult one We have chosen to develop a system in which the force and the intraocular pressure were determined directly and continuously From these data the applanated area can be calculated Therefore a hard plane applanation surface was not considered suitable for our purposes

The second alternative is to use a pressure chamber where one side is made up of a soft membrane The pressure in the chamber can be varied as desired Assuming that the physical properties of this membrane and the cornea are identical the contact area between them is plane when the pressure is the same on both sides The surface tension and the size of the contact surface do not play any role It is difficult to produce a membrane exactly identical to the cornea The pressure chamber can be modified by substituting a thin elastic and flexible membrane for the corneal type of membrane (4)

The physical forces which are required to change the shape of the thin membrane need not to be taken into consideration but a small correction for the bending forces of the cornea has to be added

After considering the different possibilities we decided to try to develop an instrument consisting of a pressure chamber where one end had a plane surface with a hole in the center This end was closed by a thin elastic and flexible membrane which could be brought in contact with the cornea In this way a plane applanated contact area was produced at the same time as the intraocular pressure was measured

An essential requirement is to be able to determine the position of the membrane accurately Different possibilities were taken into consideration

The optical method as used by Maurice was considered Ten years ago one

lar rigidity of the individual eye and otherwise an average value has to be assumed This factor of uncertainty could be eliminated if the intraocular pressure could remain constant during the tonographic procedure It is not clearly established to what extent the rate of aqueous flow facility of outflow and episcleral venous pressure, as well as blood flow, are sensitive to changes in intraocular pressure in the human eye By means of tonography at constant intraocular pressure possible errors produced by pressure changes can be studied and the importance of these errors estimated

Some procedures aimed at keeping the intraocular pressure constant during tonography have been reported Moses (6 7) added weight to the plunger of a *Schiötz tonometer in order to maintain the intraocular pressure on* a constant level He found the instruments complicated and further results were so far not reported In subsequent experiments (8 9 10) Moses developed an applanation tonography at constant intraocular pressure using the Mackay Marg tonometer The range of increase in pressure was limited to 8–12 mm Hg and the displaced volume which could be used for tonographic purpose was about 8 μl This method has considerable interest and will be further discussed in a subsequent paper

Goldmann pointed out the disadvantages of the regular tonography of Grant and discussed the possibility of performing tonography at a definite level (?)

Maurice (5) developed a recording tonometer which operates on the principle that the plunger makes a constant indentation into the cornea and the instrument measures the necessary force The decrease of the intraocular pressure is not completely eliminated but is much smaller than that found during tonography with a Schiotz tonometer

Vancea et al (12) described a procedure using an applanation tonometer to measure the pressure and an ophthalmo dynamometer to increase the pressure to desired level The displaced volume could be calculated only after determining the rigidity by differential tonometry A similar approach was used by Stepanik (11) Two separate plane surfaces were placed side by side in contact with the eye one being a regular Goldmann applanation tonometer and the other producing the amount of compression of the eye which was necessary to keep the intraocular pressure constant

In the papers reporting tonography at constant intraocular pressure valuable information concerning the problems involved has been gathered However it was felt that important unsolved problems remained before constant pressure tonography could be fully used in clinical work The purpose of the present long range research program has been to analyze various basic aspects of the problem and to try to develop an instrument for constant pressure tonography based on another principle This technique will then be applied to various problems concerning aqueous humor dynamics and blood flow in the living human eye

10 Moses R A (1967) Constant pressure applanation tonography III The relationship of tonometric pressure to rate of loss of ocular volume *Arch Ophthal* 77 181
11 Stepanik J (1968) Die Applanations Rheometrie *Klin Mbl Augenheilk* 153 253
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of us tried to use this method but the accuracy was not good enough and the project was therefore abandoned This time we were again unable to find an optical solution to the problem of determining the shape of the membrane with an accuracy sufficient for our purposes We therefore had to consider other means Instead of registering the shape of the membrane we found it better to measure the position of its centre in relation to the surrounding reference surface

A displacement transducer which was glued to a small area in the centre of the thin membrane was found to be sensitive enough for this purpose

The pressure chamber was suspended in a vertical arm which was mobile practically without friction The force pressing the membrane against the cornea can be controlled by signals from the displacement transducer in order for the membrane to remain in a constant position representing a constant intraocular pressure identical with that in the pressure chamber Knowing the force and the intraocular pressure the area of applanation can be calculated according to Imbert Fick s law The displaced intraocular volume can then be estimated by means of results obtained from a separate study concerning the relationship between the applanated area and the displaced intraocular volume (3)

This arrangement has made it possible to elevate the intraocular pressure and to keep it on a constant and known level The change in the area of applanation as well as the displaced intraocular volume can be estimated We think requirements necessary for performing applanation tonography at constant intraocular pressure can be achieved in this way

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P J Waardenburg Remarkable facts in human albinism and leukism Van Gorcum & Comp N V – Assen The Netherland 1970 103 pages 78 figures 233 references

This book is proof of the never failing academic enthusiasm of the man who pushed ophthalmology into the most rewarding period of genetic approach to differential diagnosis more than half a century ago At a time of his life when most of us will be happy if we can read a daily paper he has written a comprehensive monography on albinism and leukism which has always had his most profound interest

The book contains a short introduction on human and comparative pathology of albinism and gives references to the main biochemical problems concerned with melanin formation

The main part of the book is a discussion of general complete and incomplete albinism The biography pertaining to these diseases is complete up to 1966–67 and all articles are thoroughly discussed The value of the publication as a source of references thus cannot be overestimated The ocular features of generalized albinism are treated in great detail Dr Waardenburg points out that the structure of the iris in albinoes can be divided in two groups viz a generalized hypoplastic iris and a type presenting a close structure of the vascular layer and the annulus minor It seems that these types are genetically different The pigmentation of the pupillary border and the appearence of the pigment epithelium in cases with a rarefied stroma will be looked for by all readers of the treatise

Great emphasis is laid on the differential diagnosis between complete and incomplete albinism mostly through quotations from cases previously published It would have helped the reader though if a table presenting the differences had been included Complete albinism presents white hair throughout life and the skin remains pink Freckles are absent and tanning does not occur The visual acuity remains stationary In incomplete albinism the hair is straw coloured and may turn red or blond the skin becomes cream and slight tanning may present later in life Freckles are common The visual acuity often improves somewhat Both types of course show photophobia nystagmus foveal dysplasia and a low visual acuity

In several contexts Waardenburg returns to the intriguing family presented by Trevor Roper (1959) in which two albinoes had normally pigmented offspring The book was printed before Witkop et al (1970) had conclusively demonstrated that the male albino was tyrosinase positive and the female tyrosinase negative Waardenburg however refers to Witkop et al s important observation that albinism in a North American isolate differed biochemically from albinism in unrelated albinoes It would seem probable that tyrosinase positive and tyrosinase negative albinism is the biochemical equivalent of complete and incomplete albinism

Waardenburg is a world authority on ocular albinism He presents an exhaustive review of the literature on the subject and adds much personal experience The X linked heredity the detection of carriers through transillumination and observation of the pigmented spots in the fundus the colour vision of the affected persons and the malformation of the capillaries in the macula which is not well known is given full consideration Although reference is made to the article by Fialkow et al (1967) it does not seem to have attracted Waardenburg s interest very much that a close linkage was demonstrated between the locus for ocular albinism and the Xg locus likewise the role of the features in carriers of ocular alb n sm pertaining to Mary Lyon s theory s n t commented on

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Syndromes including generalized albinism and generalized and local leukism such as Waardenburg's syndrome the Hermansky Pudlak syndrome the Chediak Higashi syndrome the syndrome with deafness and generalized leukism (Tietz) and deafness with piebald trait (Zirprowski) as well as Xanthism are reviewed A personal opinion on the Aaland island disease in which dr Waardenburg has taken great interest would have been interesting The family described by Cross et al (1967) presenting generalized hypopigmentation microphthalmia mental retardation and progressive neurologic al deficits has evidently been published too late to be included but reference is made to a similar disease in dogs

Reading this book is like talking with the old master and as pleasant as that The style is very personal there are fervent discussions and the reader cannot help feeling involved through Waardenburg's frequent use of italics and exclamation marks. The book is a fine piece of typography and the illustrations must have been reproduced with great care considering that many of them are photographs from a time when the technique was less advanced than to day A lack of an index is moderated by an elab orate table of contents The text will be of great value to ophthalmologists workin within this specialized field

Mette Warburg

Straub Wolfgang Die ophthalmologischen Untersuchungsmetoden First volume 546 pages 542 figures Ferdinand Enke Stuttgart 1970 DM 128 –

This volume comprises methods of examining the external eye pupil slit lamp inspec tion ophthalmoscopy tonometry tonography ophthalmodynamometry *ultrasonics* X ray and isotope studies

The contents cover a wide range from commonplace eversion of the eyelid and did actic introduction into microbiology to Goldmann's detailed account of the geometrical optics of the auxiliary contact lens

Among Scandinavian studies the author quotes Oksala (ultrasonics) Krakau et al (measurements of aqueous humour cupping of the disc) Kornerup (fundus oxymetry) Boberg Ans (corneal sensibilometry) Ronne (colloidometer) Ratjen (stereoradio graphy) Schiotz and later Mahneke's tonometer testing centre

A linguistic error in quotation Nach Norn gibt es bis jetzt uber 700 erprobte Farb stoffe Should read Norn developed a vital staining method on the basis of over 700 vital stainings

The diagnostic ophthalmological methods are advancing by leaps and bounds There fore the information given in this publication is very welcome although certain details are subject to criticism and some methods are not mentioned (e g Perkins hand held tonometer Mahneke's tonometer sterilizer Abrams transpupillary transillumination Fischer Schweitzer's corneal fluorescein pattern)

This is a book to be recommended and its second concluding volume will be awaited with interest

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Index Vol 1 No 1 1970

Cole D F (London) Considerations on the Use of SI Units

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21 24 Mai 1971 Hauptthemen Ophthalmogenetik und Probleme der Hornhautchirurgie. Kongressleitung Prof Dr med habil K. E. Kruger DDR, 402 Halle (Saale) Augenklinik der Martin Luther Universitat Leninallee 8

The Management of Patients with Glaucoma

The Glaucoma Service of the Wills Eye Hospital affiliated with Temple University Health Sciences Center in Philadelph a Pennsylvania, is offering a three day course, *The Management of Patients with Glaucoma* on April 7 8 and 9 19 1 The following

niques of strabismus operations unilateral aphakia and last but not least the obligate chapter on the limitations of orthoptic exercises

All the sections are brief and concise affording up to date information about the topical problems within the various subject matters Thus the series is well suited for postgraduate orientation

K Norskov

Handbuch der medizinischen Radiologie (ed L Diethelm O Olsson F Strnad H Vieten A Zuppinger) Vol XVII Spezielle Strahlentherapie gutartiger Erkrankungen (Ed A Zuppinger & E Ruckensteiner) Pp 584 illus 76 Springer Berlin Heidelberg New York 1970 Price DM 228 – US $ 62 70

In this encyclopedia of radiation therapy of benign diseases one chapter (Pp 3??-36?) by H Oeser and E Kleberger (both from Berlin) is devoted to diseases of the eye and orbit The reader realizes immediately the close cooperation between the radiotherapist (H O) and the ophthalmologist (E K) The special radiotherapeutic conditions of the eye are carefully dealt with and the importance of the 4 mm distance of the most sensible part of the eye the equator of the lens from the limbus is stressed The reviewer agrees with most of the sober indications for radiotherapy in these benign diseases which often are self limiting inflammatory conditions better treated by cortisone Other severe eye diseases as glaucoma diabetic retinopathy and periphlebitis of the retina do not respond to radiation therapy Nevertheless there are some non neoplastic eye diseases responding well to adequate radiation therapy e g abnormal corneal vascularization rosacea keratitis resistant dendritic keratitis recurrent pterygium and sometimes Mooren s corneal ulcer and epithelial invasion of the anterior chamber The authors carefully discuss the often contradictory litterature on the subjects Sometimes the doses used by the authors themselves are missed however

In a special chapter on radiotherapy of endocrine ophthalmopathy (malignant exophthalmos) (p 185 ff) W Schlungbaum discusses the radiotherapeutic possibilities in this serious disease

The chapters on radiotherapy of eye diseases apply primarily to radiotherapeutists but it can be recommended to ophthalmologists too interested in the therapeutic possibilities

S Ry Andersen

From the University of Oslo, Department of Ophthalmology, Rikshospitalet, Oslo (Head: Professor dr. med. T. L. Thomassen) and the University of Oslo, Institut of Physics

CALCULATION OF TONOGRAPHIC OUTFLOW FACILITY

BY

MARTIN DAVANGER and ØIVIN HOLTER

Introduction

In a previous paper (*Davanger & Holter* 1967) a theoretical analysis of the pressure-time curve resulting from a disturbance of the eye's hydrodynamical equilibrium was presented. In experiments this pressure curve may be directly registered electromanometrically (*Langham & Eisenlohr* 1963), or it may be plotted by repeated tonometries (*Sæteren* 1960; *Galin et al.* 1962; *Langham* 1963; *Armaly & Halasa* 1963 ab; *Chandler* 1964). It was shown by *Davanger & Holter* (1967) that the eye's hydrodynamical parameters may be calculated from such experiments.

Clinically, however, the hydrodynamics of the eye is usually investigated by *tonography*. The tonography *curve* may be regarded as a modification of the pressure curve discussed earlier. When the tonometer is placed *on the eye*, the eye wall is indented, the initial indentation volume being V_c. As a result, the intraocular pressure increases from the equilibrium pressure P_0 to an initial value P_t. According to Friedenwald (1937) the relation between P_0, P_{t0} and V_c is given by

$$\ln (P_{t0}/P_0) = E' V_{t0} \quad (1)$$

E' is a constant related to the ocular rigidity coefficient E by $E' = E/M$, where $M = 0.4343$ is the conversion factor between Briggs and natural logarithms.

Since the intraocular pressure during tonography is higher than the equili-

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lecturers will participate Mansour F Armaly M D William R Green M D P Robb McDonald M D Kenneth T Richardson M D and George L Spaeth M D

The tuition fee is $ 150 payable to the Glaucoma Service of the Wills Eye Hospital This fee covers course tuition daily luncheon and a concert by the Philadelphia Orchestra The course which will include lectures practical demonstrations and discussions of specific cases is limited to 30 members Applications will be accepted in the order in which they are received Inquiries regarding the course should be addressed to George L Spaeth M D Director Glaucoma Service Wills Eye Hospital Philadelphia, Pennsylvania 19130

The equilibrium pressure P_o is now the equilibrium pressure during tonography. Since the episcleral venous pressure increases by an amount $\Delta P_v = 1.25$ mmHg when the tonometer is placed on the eye (*Linner* 1955) this implies an increase in the equilibrium pressure by the same amount ΔP_v and hence $P' = P_o + \Delta P_v$. The equilibrium pressure during tonography may also be influenced by a possible change in aqueous formation provoked by the tonography (*Langham* 1963).

We now substitute $\frac{dV_e}{dt} = \frac{dV_e}{dP_t}\frac{dP_t}{dt}$ in equation (6) and obtain

$$(1 - E P_t \frac{dV_e}{dP_t})\frac{dP_t}{dt} = CE P_t(P'_o - P_t) \tag{7}$$

which on integral form can be written

$$\int_{P_{to}}^{P_t} \left[\frac{1}{P_t} - \frac{1}{P_t - P'} + \frac{E P'}{P_t - P'_o}\frac{dV_e}{dP_t}\right] dP_t = CE P'_o t \tag{8}$$

where P_t is the initial pressure at $t = 0$ and P_{to} the pressure at a later time $t = t$. We perform the integration of the two first terms on the left hand side. We solve the result with respect to the outflow facility C thus obtaining

$$C = \frac{1}{t P'}\left[\frac{1}{E}\ln\frac{P_t\,(P_t - P'\,)}{P_t\,(P_t - P'\,)} + \int_{P_t}^{P_t} \frac{P'}{P_t - P'_o}\frac{dV}{dP_t}\,dP_t\right] \tag{9}$$

In order to evaluate the integral in (9) it is necessary to know the indentation volume V as a function of the pressure P_t. We shall use an empirical formula suggested by Friedenwald (1954, 1957) i.e.

$$\log P_t = B - \frac{1}{N}\log V_e \tag{10}$$

where P_t is measured in mmHg and the volume V_e in mm^3. B and N are constants determined by the plunger load.

It is more convenient to write equation (10) in the form

$$V_e = a\left(\frac{P_t}{b}\right)^{-N} \tag{11}$$

where a = antilog (BN) and b = 1 mmHg.

The values B and N (*Friedenwald* 1957) and the corresponding values of a are listed in Table 1.

brium pressure P_o aqueous outflow exceeds inflow and the intraocular pressure will decrease However as the pressure decreases the indentation volume increases with the result that the pressure drop per unit time will be smaller in a tonography curve than in the pressure decay curves discussed earlier (*Davanger & Holter* 1967)

In the previous paper it was shown that the eye s hydrodynamical parameters i e the outflow facility may be calculated from the pressure decay curve This is also the purpose of tonography

During the course of this work *McEwen et al* (1969) published a paper in which the numerical computation of outflow facility was based on essentially the same integral formulae as we have derived We have however carried the treatment one step further and evaluated the integral thus obtaining an analytical expression for the outflow facility

The tonography curve The calculation of outflow facility

During the tonography the indentation volume V_c increases at a rate $\frac{dV_c}{dt}$ This increase in the indentation volume can be regarded as an addition to the inflow F_{in} Taking into account this additional inflow the rate of change of the intraocular volume V is given by

$$\frac{dV}{dt} = F_{in} + \frac{dV_c}{dt} - F_{out} \qquad (2)$$

We assume that the aqueous outflow F_{out} is proportional to the pressure drop between the anterior chamber and the episcleral veins i e

$$F_{out} = C(P_t - P_v) \qquad (3)$$

where P_t is the intraocular pressure during tonography P_v is the episcleral venous pressure and the constant of proportionality C is the outflow facility

The relation between F_{in} and P is given by

$$F_{in} = C(P_o - P_v) \qquad (4)$$

By substituting F_{in} and F_{out} from the equations (3) and (4) in equation (2) we obtain

$$\frac{dV}{dt} = C(P_o - P_t) + \frac{dV_c}{dt} \qquad (5)$$

By using the differential form of Friedenwald s formula equation (1) we can rewrite equation *(5) in the form*

$$\frac{dP_t}{dt} = CE\,P_t(P_o - P_t) + E\,P_t\frac{dV}{dt} \qquad (6)$$

We obtain n from $n = N - 2$ where N is given in Table 1 For the case with plunger load 5 5 g we may put $n \approx 0$ and thus equation (15) is further reduced to

$$C \approx \frac{1}{t_n P'_o}\left\{ \left(\frac{1}{E} + Na\left(\frac{b}{P'_o}\right)^2 \ln \frac{P_{tn}(P_t - P'_o)}{P_{to}(P_t - P_o)}\right.\right.$$

$$\left.\left. - Na\left(\frac{b}{P_o}\right)^2 \left[\frac{P_o}{P_{tn}}\left(1 + \tfrac{1}{2}\frac{P}{P_{tn}}\right) - \frac{P_o}{P_{to}}\left(1 + \tfrac{1}{2}\frac{P_o}{P_{to}}\right)\right]\right\} \qquad (16)$$

Discussion and results

The computations of outflow facility from equation (14) is in principle straightforward For the different plunger loads we use the constant in Table 1 For the scleral rigidity we use the average value $E = 0\,0495$ The equilibrium pressure P_o is given in terms of P_{to} by

$$P_o = P_{to}\, e^{-E V_{co}} + \Delta P_v \qquad (17)$$

where

$$V_o = a\left(\frac{P_t}{b}\right)^{-N} \qquad (18)$$

The tables for outflow facility give C for different changes in the scale reading R of the tonometer during the time t_n The connection between scale reading R and the pressure P_t is given by

$$P_t = \frac{W}{0\,107 + 0\,0138\,R}$$

where W is the plunger load (*Friedenwald* 1957 *Gloster* 1966)

We have computed a set of tables for C, with the standard time interval $t_n = 4$ min For completness they are given in the Tables 2 to 5 for the four different plunger loads *Tables* 2 and 3 give results identical to those of McEwen et al (1969) For plunger load 5 5 *g we have in* Fig 1 given a graphical exposition of the results presented in Table 2 The deviations from the results obtained by Grant s formula is illustrated in Fig 2

In equation (15) we have given an approximate formula for C The accuracy of this formula has been *estimated* numerically by comparison with the exact formula (14) and over the whole range of parameter values investigated the

Table 1

Plunger load	B	N	a
5 5 g	2 029	2 016	12310
7 5 g	2 092	2 174	35390
10 g	2 160	2 300	92900
15 g	2 262	2 455	357500

Substitution of the expression (11) for V_c in equation (9) yields

$$C = \frac{1}{t_n P_o}\left[\frac{1}{E}\ln\frac{P_{tn}(P_{to}-P_o)}{P_{to}(P_{tn}-P_o)} - aN\left(\frac{b}{P_o}\right)^N I\right], \qquad (12)$$

where I is the definite integral

$$I = \int_{P_{to}}^{P_{tn}} \left(\frac{P_o}{P_t}\right)^{N+1} \frac{dP_t}{P_t-P_o} \qquad (13)$$

The expression for C which was used by McEwen et al (1969), can be transformed to the form (12) by suitable integrations and by introducing $E = 0\ 0495$

As shown in the Appendix the integral (13) can be evaluated the result being an infinite sum By using the equations (A4) and (A6) we obtain from equation (9) the general expression for the outflow facility i e

$$C = \frac{1}{t_n P_o}\left\{\frac{1}{E}\ln\frac{P_{tn}(P_{to}-P_o)}{P_{to}(P_{tn}-P_o)} - Na\left(\frac{b}{P_o}\right)^N \sum_{s=1}^{\infty}\frac{1}{N+s}\left[\left(\frac{P_o}{P_{tn}}\right)^{N+s} - \left(\frac{P_o}{P_{to}}\right)^{N+s}\right]\right\} \qquad (14)$$

An approximate expression for C which is simpler to apply since it does not involve any summation, is obtained by using (A10) i e

$$C \approx \frac{1}{t_n P_o}\left\{\frac{1}{E}\ln\frac{P_{tn}(P_t-P_o)}{P_{to}(P_{tn}-P_o)} - Na\left(\frac{b}{P}\right)^N\left(\left(\frac{P_o}{P_{tn}}\right)^n\left[\left(1-n+n\frac{P_{tn}}{P_o}\right)\ln\left(1-\frac{P_o}{P_{tn}}\right)\right.\right.\right.$$

$$\left. +n+\left[1-\tfrac{1}{2}n+\tfrac{1}{2}\left(1-\frac{n}{3}\right)\frac{P_o}{P_{tn}}\right]\frac{P_o}{P_{tn}}\right] - \left(\frac{P_o}{P_{to}}\right)^n\left[\left(1-n+n\frac{P_{to}}{P_o}\right)\ln\left(1-\frac{P_o}{P_{to}}\right)+n\right.$$

$$\left.\left.\left. + \left[1-\tfrac{1}{2}n+\tfrac{1}{2}\left(1-\frac{n}{3}\right)\frac{P_o}{P_{to}}\right]\frac{P_o}{P_{to}}\right]\right)\right\} \qquad (15)$$

deviation is less than 1 %. In view of the uncertainties attached to the different numerical constants this should therefore be a valid formula for C.

One of the constants which show significant deviations for individual eyes is the scleral rigidity E. When for an eye E deviates substantially from the average value the value of C obtained from standard tables is not useful. The computation of C should then be performed directly from the basic formulae (14) (or (15)). To facilitate such computations we have numerically evaluated the function A (x) as defined in equation (A8). The result is shown in Fig. 3 where A is plotted as a function of P_t/P'. In order to find the value of I in equation (12) it is necessary to determine the pressure P_{to} and P_{tn} and the equilibrium pressure $P \approx P + \Delta P_v$. P can either be computed from equa-

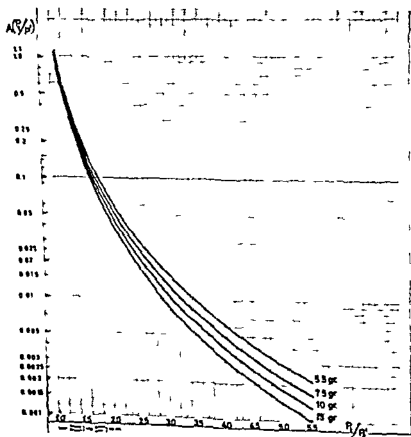


Fig. 3
The relation between P_t/P and $A(P_{tn}/P')$

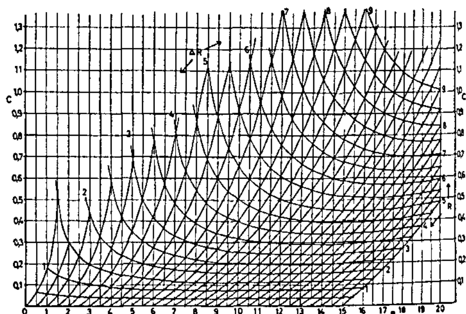


Fig 1
The relation between outflow facility C and the change ΔR in scale reading R 55 gr w C is found by following the curve from $R = R_0$ to the intercept of the vertical line $R = R_4$ R_0 and R_4 are scale readings at 0 and 4 min respectively

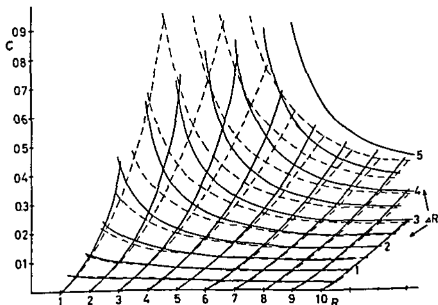


Fig 2
The discrepancy between the new C values —— and those obtained by using Grant s formula – – – –

tion (17) with the new E value or obtained directly by applanation tonometry. When these pressures have been determined the value of I is given by

$$I = A(P_{tn}/P_o) - A(P_{to}/P_o)$$

where the values $A(P_{tn}/P_o)$ and $A(P_{to}/P_o)$ can be obtained directly from the appropriate curve in Fig 3. This method for computation of C can also be used for tonography curves lasting longer or shorter than the standard time 4 min.

Summary

A formula for tonographic outflow facility is derived on the basis of a review of the theory of tonography. Tables of C values calculated from the new formula are given. Errors introduced by previous less accurate methods of calculation are eliminated.

Appendix

In order to evaluate the integral (13) explicitly we introduce the variable x defined by

$$x = \frac{P_o}{P_t} \quad dP_t = -\frac{P_o}{x^2}\,dx \tag{A1}$$

Equation (13) can then be written

$$I = \int_{P_o/P_{to}}^{P_o/P_{tn}} \frac{x^N}{1-x}\,dx \tag{A2}$$

In the following we drop the integration limits and consider the indefinite integral

$$A(x) = \int \frac{x^N}{1-x}\,dx \tag{A3}$$

in terms of which

$$I = \left[A(P_o/P_{tn}) - A(P_o/P_{to})\right] \tag{A4}$$

Since $x<1$ we may use the summation formula for a geometric series to obtain

$$\frac{1}{1-x} = \sum_{s=1}^{\infty} x^{s-1} = 1 + x^2 + x^3 + \qquad \text{(A5)}$$

We introduce this series into (A3) and obtain

$$A(x) = \sum_{s=1}^{\infty} \int x^{N+s-1}\, dx = \sum_{s=1}^{\infty} \frac{1}{N+s} x^{N+s} \qquad \text{(A6)}$$

When this sum for A(x) is substituted in equation (A4) we obtain the result given in equation (14). The sum (A6) may exhibit slow convergence and in numerical computations it may be necessary to include a large number of terms. It is however possible to perform parts of the summation directly. For this purpose we write $N = N_0 + n$ where N_0 is the integer closest to N and hence $n \leq 1/2$. We now write the coefficient in (A6) in the form

$$\frac{1}{N+s} = \frac{1}{N_0+s} - \frac{n}{(N_0+s)(N_0+s+1)} + \frac{n(n-1)}{(N_0+s)(N_0+s+1)(N_0+s+n)} \qquad \text{(A7)}$$

We introduce this expression into equation (A6) and employ the following series expansions (*Ryshik & Gradstein* 1963, p. 42)

$$\sum_{s=1}^{\infty} \frac{1}{s} x^s = -\ln(1-x)$$

$$\sum_{s=1}^{\infty} \frac{x^s}{s(s+1)} = 1-(1-1/x)\ln(1-x)$$

and obtain

$$A(x) = -x^n \left[(1-n+n/x)\ln(1-x) + n + \sum_{s=1}^{\infty} \frac{1}{s}\left(1-\frac{n}{s+1}\right)x^s \right]$$

$$+ n(1-n)x^n \sum_{s=1}^{\infty} \frac{x^{N_0+s}}{(N_0+s)(N_0+s+1)(N_0+s+n)} \qquad \text{(A8)}$$

With the values given in Table 1, $N_0 = 2$ for all plunger loads. Since $n \leq 1/2$ and $s \geq 1$ we obtain for the ratio between the last and first term in (A8)

$$\frac{n(1-n)}{(N_0+s+1)(N_0+s+n)} < 2\,10 \ll 1 \qquad \text{(A9)}$$

and hence the error introduced by neglecting the last term in (A8) is small Thus with $N_0=2$ we arrive at the approximate expression

$$A(x) \approx -x^n\left\{(1-n+n/x)\ln(1-x)+n+\left[1-\tfrac{1}{2}n+\tfrac{1}{2}(1-\tfrac{n}{3})x\right]x\right\} \qquad (A10)$$

In particular for $n \ll 1/$ as is the case for 5 5 gr plunger load we obtain

$$A(x) \approx -\ln(1-x) + x + x/2 \qquad (A11)$$

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Aus der Universitäts-Augenklinik Jena/DDR
(Direktor Prof. Dr. med. habil. A. Heydenreich)

DIE VARIABILITÄT DER CHORIOIDITIS JUXTAPAPILLARIS JENSEN UND IHRE BEDEUTUNG FÜR DIE DIFFERENTIALDIAGNOSE DER OPTICUSPROZESSE

VON

W. KÖHL

Die Opticusprozesse gehören auch heute noch zu den wichtigsten und differentialdiagnostisch schwierigsten Erkrankungen des Auges. Sie erfordern die ganze ärztliche Kunst, weil die richtige Diagnose nicht nur für die Erhaltung der Sehkraft, sondern auch für das Leben des Patienten von entscheidender Bedeutung sein kann (vgl. die Tabelle). Hier muss jede mögliche Hilfe ergriffen werden, und die Fluoreszenzangiographie kann dabei Entscheidendes leisten (*Jütte* & *Lemke* 1968, *Wessing* 1968, *Shikano* & *Shimi u.* 1970). Relativ einfach gestaltet sich hiermit die Abgrenzung gegen die Pseudopapillitis, da sich die Drusenpapille, die Pseudopapillitis hyperopica und physiologische Varianten fluoreszenzangiographisch sehr gut darstellen lassen (*Weinstein*). Schwerer sind die Abgrenzungen der entzündlichen Veränderungen, der Durchblutungsstörungen und der Stauungspapille. Ebensogrosse Schwierigkeiten kann die Diagnostik der Chorioiditis juxtapapillaris *Jensen* bereiten.

Es soll anhand von 4 Fällen darüber berichtet werden.

1. Pat. Erika K.

Die 40jährige Patientin kam wegen grauen Flecken auf dem linken Auge in die Sprechstunde.

Eingegangen am 14. September 1970.

Visus rechts + 0,75 sph = 5/4
Visus links + 2,0 sph = 5/4

Papille rechts insgesamt etwas unscharf, temporal leicht prominent. Links völlig unscharfe Papille mit Kapillarektasien und -neubildungen. Die Vorderabschnitte waren unauffällig; im Gesichtsfeld fand sich links ein sehr kleiner, zum Zentrum ziehender Defekt temporal unten, der nach 14 Tagen bereits wieder verschwunden war. Es bestand dringender Verdacht auf Stauungspapille durch Tumor. Ophthalmoskopisch zeigte sich im Fluoreszenzangiogramm links deutlich ein Farbstoffaustritt temporal unten. (Siehe auch Abb. 1 und 2.)

Abb. 1: Fluoreszenzangiogramm nach 15 sec. Die Kapillaren sind reichlich geschlängelt. Mikroaneurysmen besonders am Papillenrand; sie reichen aber nicht über 1/3 des PD. Die peripapillären Kapillaren sind deutlich sichtbar.

Abb. 2: Nach 27 sec. noch sehr intensive diffuse Anfärbung der Papille.

Die Neovaskularisation auf der Papille bei 5 h nahm in den nächsten Wochen noch ziemlich zu. Der Farbstoffaustritt verstärkte sich. Es wurde die Diagnose Chorioiditis juxtapillaris Jensen links gestellt.

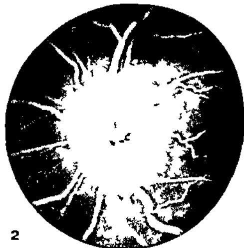
Am rechten Auge handelte es sich um eine Pseudopapillitis. Unter intensiver Therapie, besonders mit retrobulbären Oradexoninjektionen, kam es zu einer deutlichen Herdbildung auf der Papille bei 5 h, die sich immer besser abgrenzte. Nach 7 Wochen war noch eine zarte Bindegewebsproliferation im Entzündungsgebiet festzustellen. Das Gesichtsfeld war normal.

Der Visus betrug rechts/links 5/4.

2. Pat. Ute H.

Die 16jährige Patientin suchte wegen Schleiersehen am rechten Auge den Augenarzt auf. Visus rechts: 5/5 p, Visus links: 5/4. Rechts war die Papille unscharf mit leichter


1


2

Fall 1 Erika K.

Abb. 1 Fluoreszenzaufnahmen des linken Auges nach 15 sec.
Abb. 2 Fluoreszenzaufnahmen des linken Auges nach 27 sec.

Prominenz im oberen Pol Ein Gesichtsfeldausfald bestand nicht Es wurde eine Neuritis nervi optici rechts angenommen Links bestand ein regelrechter Augenbefund Im Fluoreszenzangiogramm kam es zu einem typischen sektorenformigen Fluoreszeinaustritt zwischen 1–3 h.

Abb 3 zeigt die Anfarbung bereits nach 5 sec. bevor die Retinagefasse gefullt sind Am Papillenrand farben sich zwei Stellen in Gefassnahe besonders stark an, die ophthalmoskopisch als grauweisse Verdichtungen der oberen Netzhautschichten imponierten.

Abb 4 gibt das Fluoreszenzbild nach 3 Minuten wieder Durch die diffuse Anfarbung ist praktisch die ganze Papille bedeckt.

Nach Durchfuhrung einer Kur in der Augenheilstatte Masserberg war der herdformige Prozess von 1–3 h abgeheilt, es war nur ein leichter Bindegewebsschleier in diesem Bereich zuruckgeblieben Der Visus betrug rechts 5/5 p links 5/4

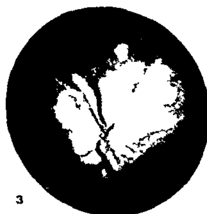
3 Pat. Thomas H

Der 13jahrige Thomas H wurde mit der Diagnose Zentralvenenthrombose rechts stationar eingewiesen

Visus rechts 5/15 p

Visus links 5/5 p

Rechts unauffallige Vorderabschnitte. Glaskorper feine staubige Trubungen Papille 1½ Dptr prominent temporal unten weissliches Ödem zentrale Sanguinationen gestaute Venen gestaute Venolen (s a Oosterhuis) und Arteriolen Makulaodem und Sternfigur An fast allen grosseren Venenasten ausgedehnte flachige Sanguinationen. In der Universitats Kinderklinik wurden Blutgerinnungsstorungen und eine Allgemeinerkrankung ausgeschlossen, in der Neurologischen Universitats Klinik das Vorliegen eines Hirntumors Die Fluoreszenzaufnahmen am ?5 1 1968 zeigten nach 2 sec.





Fall 2 Ute H

Abb 3 Fluoreszenzaufnahmen des rechten Auges nach 5 sec

Abb 4 Fluoreszenzaufnahmen des rechten Auges nach 3 Min

Visus rechts + 0 75 sph = 5/4
Visus links + 2 0 sph = 5/4

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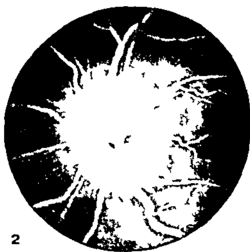
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Der Visus betrug rechts/links 5/4

2 Pat Ute H

Die 16jährige Patientin suchte wegen Schleiersehen am rechten Auge den Augenarzt auf Visus rechts 5/5 p Visus links 5/4 Rechts war die Papille unscharf mit leichter





Fall 1 Erika K

Abb 1 Fluoreszenzaufnahmen des linken Auges nach 15 sec
Abb 2 Fluoreszenzaufnahmen des linken Auges nach 27 sec

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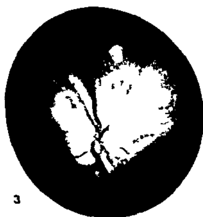
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3


4

Fall 2 Ute H

Abb 3 Fluoreszenzaufnahmen des rechten Auges nach 5 sec
Abb 4 Fluoreszenzaufnahmen des rechten Auges nach 3 Min

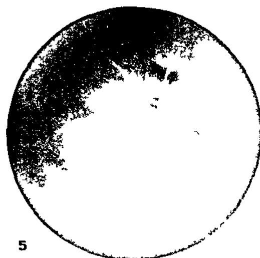
Abb 5 Fluoreszenzangiogramm vor Gefassfullung Sektorenformige Anfarbung nasal unten

Abb 6 Fluoreszenzangiogramm nach 14 sec Die Fluoreszein Anfarbung verdeckt grosstenteils die Kapillaren die Aneurysmen und Sanguinationen sind deutlich sichtbar

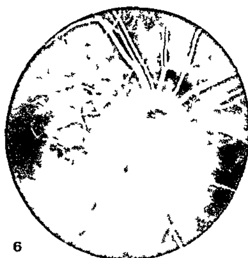
Abb 7 Nach 22 sec ist der Farbstoff noch weiter ausgetreten und verdeckt weitere Einzelheiten Die intensive Anfarbbarkeit der grossen Gefasse erklart auch die starken Blutaustritte

Abb 8 Nach 2 Minuten noch starke diffuse Farbung der ganzen Papille

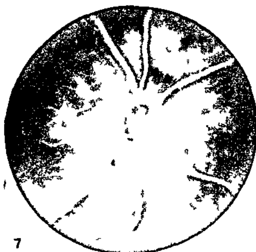
Auf Grund der Fluoreszenzangiographie wurde die Diagnose Chorioiditis juxtapa



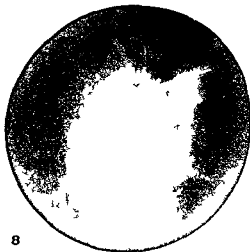
5



6



7



8

Fall 5 Thomas H (aus *Jutte & Lemke* 1969)

Abb 5 Fluoreszenzaufnahmen des rechten Auges nach 2 sec

Abb 6 Fluoreszenzaufnahmen des rechten Auges nach 14 sec

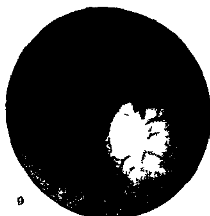
Abb 7 Fluoreszenzaufnahmen des rechten Auges nach 22 sec

Abb 8 Fluoreszenzaufnahmen des rechten Auges nach 2 Min

pillaris Jensen gestellt Im Gesichtsfeld lag ein grosser temporal oberer Ausfall vor Unter intensiver Therapie heilte der Prozess gut mit einer kleinen peripapillaren Narbe ab (siehe Abb 9–11) der Gesichtsfelddefekt blieb unverandert Der Visus war bei der Entlassung rechts/links 5 4 p

Abb 9 Nach 10 Wochen Fluoreszenzangiogramm nach 7 sec keine Anfarbung vor der Gefassfullung mehr sichtbar

Abb 10 Fluoreszenzangiogramm nach 26 sec. Das Kapillarverhalten ist wieder regular dafur zeigt sich fleckige Aufhellung im Bereich der Aderhaut Es ist zur narbigen Ausheilung und zu Pigmentblattdefekten in der Chorioidea gekommen



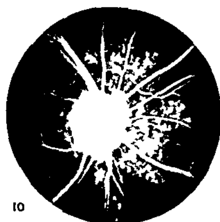




Abb 9 Fluoreszenzaufnahmen des rechten Auges in der 10 Woche nach Krankheitsbeginn nach 7 sec

Abb 10 Fluoreszenzaufnahmen des rechten Auges in der 10 Woche nach Krankheitsbeginn nach [illegible] sec

Abb 11 Fluoreszenzaufnahmen des rechten Auges in der 10 Woche nach Krankheitsbeginn nach [illegible] Min

Tabelle 1
Differentialdiagnose des Papillenodems

Pseudopapillitis	a) Phys Varianten b) Pseudopapillitis hyperopica c) Drusenpapille
Durchblutungsstorungen	a) Arteriosklerotische ischamische Papille b) Partielle und vollstandige Zentralvenenthrombose (besonders in Fruhstadium) c) Retinopathia angiospastica (im Spatstadium)
Entzundliche Veranderungen	a) Papillitis b) Chorioiditis juxtapapillaris Jensen c) chron Cyclitis mit Begleitpapillitis d) IRVINE GASS Syndrom
Ungleichgewicht zwischen Druck von aussen und Augeninnendruck	a) Stauungspapille b) Stauungspapille e vakuo

Abb 11 Nach 2 Minuten ist der zarte Exsudatschleier von 5–7 h geringfugig angefarbt die Aderhautfluoreszenz ist deutlicher geworden bei 5–6 h im Bereich der peripapillaren Narbe am ausgepragtesten

4 Pat Hildegard F

Die 55jahrige Frau F kam mit einer akuten Neuritis nervi optici rechts zur stationaren Aufnahme Der Visus betrug rechts 1/50 links 5/4 Rechts war die Papille in toto unscharf und leicht prominent In der Makula fand sich ein starkes Ödem und Sternfigur Links altersgemasser Augenbefund Im Fluoreszenzangiogramm wurde rechts ein intensiver Farbstoffauttritt bei 10–11 h an dessen Stelle sich erst nach einigen Tagen ein Herdprozess abzeichnete bemerkt Das Fluoreszein trat vor der retinalen Gefassfullung aus und farbte nach einigen Minuten intensiv die ganze Papille an (Aus technischen Grunden konnen fur diesen Fall leider keine Bilder vorgelegt werden)

Bei den 4 Patienten die mit der Diagnose Stauungspapille Neuritis nervi optici und Zentralvenenthrombose zur Behandlung kamen konnte durch wiederholte ophthalmoskopische Fluoreszenzkontrollen und Fluoreszenzangiographien schon sehr frühzeitig die Diagnose Chorioiditis juxtapapillaris Jensen gestellt werden Als entscheidende Kriterien gelten dabei vor allem der intensive sektorenformige Farbstoffaustritt auf der Papille noch bevor sich ein Herdprozess abzeichnet die Fluoreszenzfarbung im Herdgebiet in der Fruhphase noch vor der retinalen Gefassfullung erst in einem grosseren Intervall kommt es dann zur Anfarbung auf der ganzen Papille

Zusammenfassung

Es wird uber 4 Falle mit Verdacht auf Stauungspapille Zentralvenenthrombose und 2 X Neuritis nervi optici berichtet bei denen mit Hilfe wiederholten oph thalmoskopischen Fluoreszenzangiographien und Fluoreszenz Fotos sehr fruh zeitig die Diagnose Chorioiditis juxtapapillaris Jensen gestellt werden konnte Die Krankheitsverlaufe werden kurz dargestellt und auf die differentialdiagno stischen Schwierigkeiten eingegangen sowie auf die spezifischen Merk male mit der Fluoreszenzangiographie hingewiesen

Unserer Fotomeisterin Frau Waltraud Krausse mochte ich fur die Anferti gung der Fluoreszenzfotos herzlichen Dank sagen

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Dr med W Kuhl 69 Jena/DDR Univ Augenklinik Jena Bachstr 18

From the University of Bergen School of Medicine
Department of Ophthalmology
(Head Professor Torstein I Bertelsen M D)

THE FREQUENCY OF FIBRILLOPATHIA EPITHELIOCAPSULARIS (SO-CALLED SENILE EXFOLIATION OR PSEUDOEXFOLIATION) IN PATIENTS WITH OPEN ANGLE GLAUCOMA

BY

HENRY AASVED

The purpose of this study was to investigate the frequency of fibrillopathia epitheliocapsularis (so-called senile exfoliation or pseudoexfoliation of the anterior lens capsule) in groups of patients representing different degrees of severity of open angle glaucoma

Earlier investiations of glaucoma materials have shown variations in the frequency of fibrillopathy from 0 per cent (*Leydhecker* 1960) to 93 per cent (*Horven E* 1935) A tabular survey of earlier studies can be found in another work by the present author (*Aasved* 1969) The reason for this great variation is not known

Among the population as a whole the author has shown that there is probably no significant geographical variation in the frequency of fibrillopathy (*Aasved* 1969) It was pointed out that the results might be influenced by several factors such as interest of the examiner accuracy in investigation examination conditions and the size of the materials This applies also to glaucoma materials In the population as a whole a definite increase in frequency was found with increasing age (*Aasved* 1969) That the same factor may influence the glaucoma materials was also suggested in earlier studies (*Lindberg* 1917 *Busacca* 1928 *Horven E* 1935 *Horven I* 1966) Several authors have described familiar oc

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currence of fibrillopathy (*Vogt* 1930 *Gifford* 1951 *Amalric et al* 1960 *Tarkkanen* 1962 *Tarkkanen et al* 1965 *Bertelsen* 1966 *Klouman* 1967 *Sæbo* 1961 *Aasved* 1969 *Knape & Paitta* 1970) A hereditary factor may therefore influence the frequency of fibrillopathy in local population groups

In addition the type and character of the glaucoma may be of importance

The relatively close relation between fibrillopathy and glaucoma applies only to open angle and not to narrow angle glaucoma (*Baumgart* 1933 *Gradle & Sugar* 1940 and 1947 *Holst* 1947 *Horven E* 1948 *Ross* 1949 *Gillies* 1962 *Tarkkanen* 1962 *Lowe* 1964) The relative incidence of these two types of glaucoma in the materials may thus influence the fibrillopathy frequency

It has been asserted that capsular glaucoma (open angle glaucoma associated with fibrillopathy) is more serious than simple glaucoma (*Vogt* 1930 *Gr ed iel ski* 1931 *Blaickner* 1932 *Gradle & Sugar* 1947 *Joannides et al* 1961 *Gillies* 1962 *Tarkkanen* 1965 *Horven I* 1966) This is confirmed by another study by the present author (Aasved) Consequently one might expect to find a relatively high frequency of fibrillopathy in groups of patients suffering from advanced glaucoma in comparison with groups of lighter cases This assumption is of special importance as different surveys in the past may represent different degrees of severity according to the method of selecting the patients The data have been collected from mass screenings ordinary eye practices out patient clinics eye departments and from patients subjected to glaucoma operations (cf table 2 *Aasved* 1969)

In the present study an analysis has been made to determine the influence of sex and age on the fibrillopathy frequency and whether patient groups with relatively severe open angle glaucoma show higher frequencies of fibrillopathy than groups of lighter cases It will further be discussed whether these factors may explain in whole or in part the varying frequencies demonstrated in different groups of patients with glaucoma

Finally a general evaluation of the frequency of fibrillopathy among patients with open angle glaucoma in Norway will be given

Material and Methods

The material was collected in Bergen Norway and embraces persons above the age of 50 years The investigation includes only patients with primary open angle glaucoma (chronic simple glaucoma) and patients with open angle glaucoma associated with fibrillopathia epitheliocapsularis (capsular glaucoma)

The examinat on f r *fibrillopathy* was made with a slitlamp in a dark room If no f br ll pathy coul l be demonstrated with the pup ls at ordinary s ze the examination

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miotics + adrenalin + acetazolamid) 81 1 per cent of these patients had optic nerve damage

4? patients with *unilateral absolute glaucoma or nearly absolute glaucoma* (profound optic nerve damage but some light perception still present) Thus 100 per cent of these patients had optic nerve damage

The in patient group included 17 men and 16 women from the mass screning and out patient groups who were admitted to the eye department during th above mentioned period In calculating the total number of glaucoma patients examined correction has been made for this double registration

The total material thus consists of 444 patients 239 men and 205 women

Both for the total material and the different patient groups the frequency of fibrillopathy has been estimated on the basis of the number of patients and not on the number of glaucomatous eyes

A correlation between the fibrillopathy incidence and sex age and severity of the glaucoma is firstly sought for the total material as such The results of this primary analysis have been applied to the different patient groups correction being made for uneven distribution of the influencing factors

As this survey comprises relatively few patients an indirect method of correction has been used (*Hill* 1961)

Table 1 shows the sex and age distribution of the patients in the different groups and in the total material

Results

Table 2 shows the incidence of fibrillopathy in all the examined glaucoma patients The frequency was somewhat higher in women (36 1 per cent) than in men (30 1 per cent) This difference might however have arisen by chance ($P > 0\ ?0$) After making allowance for a slight difference in the age distribution between the two sexes the frequency was calculated at 33 9 per cent in women and 31 6 per cent in men This correction was made by *using the total* material as standard Likewise a slight difference in the frequency among males as opposed to females in each patient group may also have arisen by chance ($P > 0\ ?0$)

These results seems to indicate that the sex factor is of little or no importance in this context It therefore seems justifiable to disregard this factor and the two sexes are presented together in the following tables

Table ? demonstrates however an increasing frequency of fibrillopathy at increasing ages When comparing different glaucoma surveys with regard to the frequency of fibrillopathy due *consideration* will therefore have to be given to the age distribution

was repeated after dilatation with homatropin or cyclopentolate hydrochloride (Cyclogyl®) Patients with or without fibrillopathy were considered to suffer from glaucoma when fullfilling at least *one of the following criteria*

1 Spontaneous intraocular pressure of 20 mm Hg or more combined with excavation of the optic disc to the edge and/or visual field defect characteristic of glaucoma

2 Spontaneous intraocular pressure of 25 mm Hg or more measured on at least 3 occasions

3 Intraocular pressure of 20 mm Hg or more combined with water drinking test which elevates the pressure by at least 10 mm Hg and/or tonography with out flow facility equal to or less than 0 12

The intraocular pressure was measured by applanation tonometry or with a standardized Schiotz weight tonometer using the calibration scale of 1955

The survey embraces *three patient groups* which on the average show an increasing degree of severity of glaucoma namely a *mass screening group* an *out-patient group* and a *group of in-patients*

The patients are divided into *three subgroups* according to the severity as judged by ophthalmoscopy and visual field examinations *patients with optic nerve damage* showing excavation of the optic discs to the edge and/or visual field defects characteristic of glaucoma in one or both eyes *patients without optic nerve damage* having normal optic discs and visual fields and *unclassifiable patients* embracing a few cases in which the state of the optic discs and the visual fields could not be assessed

The mass screening group consists of 103 newly diagnosed cases found among 5446 persons above the age of 50 collected by mass screening at 85 different industrial firms and 30 different old age homes in Bergen 24 3 per cent of these patients had optic nerve damage

The out patient group consists of 97 patients treated at the out patients clinic of the Department of Ophthalmology University of Bergen from the opening of the clinic on September 5th 1961 to January 1st 1969 Tonometry is here carried out as a matter of routine for all patients above the age of 40 unless there are special contra indications Patients in whom glaucoma was diagnosed during the above mentioned mass screening were not included in this group Neither does this group include patients who had been admitted to an eye hospital for glaucoma prior to the examination at the out patients clinic 60 per cent of these patients had optic nerve damage

The in patient group consists of 277 patients admitted to the Department of Ophthalmology University of Bergen from the opening of the Department on September 5th 1961 to January 1st 1969 This group consists mainly of cases in which the intraocular pressure had not been satisfactory regulated by ambulant treatment 70 8 per cent of these patients had optic nerve damage

The following are *subgroups of the in patient group*

90 patients on whom *operations for glaucoma* have been performed as it was not possible to normalize the intraocular pressure by medication (*ordinarily*

Table 2

Frequency of fibrillopathy in the total number of patients with open angle glaucoma

Age Years	Males Total No pat	Males Fibr incidence No pat	Males Fibr incidence per cent	Females Total No pat	Females Fibr incidence No pat	Females Fibr incidence per cent	Both sexes Total No pat	Both sexes Fibr incidence No pat	Both sexes Fibr incidence per cent
50–59	48	5	10.4	29	4	13.8	77	9	11.7
60–69	90	19	21.1	64	18	28.1	154	37	24.0
70–79	73	33	45.2	76	34	44.7	149	67	45.0
80–89	[illegible]8	15	53.6	30	18	50.0	64	33	51.6
Total	239	[illegible]	30.1	205	74	36.1	444	146	32.9

Table 1

Sex and age distribution in different groups of patients with open angle glaucoma In the column marked total correction has been made for double registration of 17 men and 16 women see text

Sex	Mass screening		Out patients		In patients		Glaucoma operations		Absolute glaucoma		Total	
	No pat	per cent	No pat	per cent	No pat	per cent	No pat	per cent	No pat	per cent	No pat	per cent
Male	63	61 2	52	53 6	141	50 9	46	51 1	22	52 4	239	53 8
Female	40	38 8	45	46 4	136	49 1	44	48 9	20	47 6	205	46 2
Both sexes Age Years												
50–59	33	32 1	17	17 5	30	10 8	13	14 4	2	4 8	77	17 3
60–69	41	39 8	44	45 4	87	31 4	24	26 7	8	19 0	154	34 7
70–79	13	12 6	24	24 7	120	43 3	41	45 6	20	47 6	149	33 6
80–89	16	15 5	12	12 4	40	14 5	12	13 3	12	28 6	64	14 4
Total	103	100 0	97	100 0	277	100 0	90	100 0	42	100 0	444	100 0

Table 4

Recorded incidence of fibrillopathy in different groups of patients with open angle glaucoma

Age Years	Mass screening Total No pat	Fibr incid No pat	per cent	Out patients Total No pat	Fibr incid No pat	per cent	In patients Total No pat	Fibr incid No pat	per cent	Glauc operations Total No pat	Fibr incid No pat	per cent	Absolute glaucoma Total No pat	Fibr incid No pat	per cent
50–59	33	3	9.1	17	2	11.8	30	6	20.0	13	4	30.8	2	2	100.0
60–69	41	5	12.2	44	14	31.8	87	4	27.6	24	9	37.5	8	5	62.5
70–79	13	4	30.6	24	9	37.5	120	58	48.3	41	28	68.3	20	14	70.0
80–89	16	5	31.3	12	5	41.7	40	25	62.5	12	8	66.7	12	10	83.3
Total	103	17	16.5	97	30	30.9	277	113	40.8	90	49	54.4	42	31	73.8
Age corrected frequencies			0.0			33.4			37.5			50.0			59.0

Table 3 shows the incidence of fibrillopathy in patients with and without signs of optic nerve damage

The state of the optic nerve was unclassifiable in 10 patients 2 with fibrillopathy From the mass screening/out patient groups 25 patients with optic nerve damage 19 with fibrillopathy and 8 patients without optic nerve damage 2 with fibrillopathy were admitted to the eye department

The table shows that both groups had an increasing fibrillopathy frequency with increasing age The frequency was however much higher in patients with optic nerve damage (44 6 per cent) than in patients without optic nerve damage (16 5 per cent) This difference have not arisen by chance ($P < 0\ 0005$) A similar difference can be demonstrated for all age groups Correction has been made for a slight variation in the age distribution in the two groups but the corrected frequencies still show a marked difference (40 1 per cent and 19 8 per cent) The frequency for the total material was used as a standard

It is consequently of the utmost importance to know the severity of the glaucoma when calculating the fibrillopathy frequency in a glaucoma survey

Prior to a comparison between different glaucoma surveys a correction for uneven age distribution and uneven distribution of severity of glaucoma must be carried out Such a correction has been made for the different patients groups in the present study

Table 4 shows the frequency of fibrillopathy within each group of patients In all groups an increase in age resulted in a higher frequency of fibrillopathy

The table shows that there was a considerable variation in the frequency of

Table 3

Frequency of fibrillopathy in glaucomatous patients with and without optic nerve damage

Age Years	With optic nerve damage			Without optic nerve damage		
	Total	Fibr incidence		Total	Fibr incidence	
	No pat	No pat	per cent	No pat	No pat	per cent
50–69	27	7	25 9	49	2	4 1
60–69	77	26	33 8	74	11	14 9
70–79	109	53	48 6	37	12	32 4
80–89	45	29	64 4	16	4	25 0
Total	258	115	44 6	176	29	16 5
Age corrected frequencies			40 1			19 8

Table 4

Recorded incidence of fibrillopathy in different groups of patients with open angle glaucoma

Age Years	Mass screening Total No pat	Mass screening Fibr incid No pat	Mass screening Fibr incid per cent	Out patients Total No pat	Out patients Fibr incid No pat	Out patients Fibr incid per cent	In patients Total No pat	In patients Fibr incid No pat	In patients Fibr incid per cent	Glauc operations Total No pat	Glauc operations Fibr incid No pat	Glauc operations Fibr incid per cent	Absolute glaucoma Total No pat	Absolute glaucoma Fibr incid No pat	Absolute glaucoma Fibr incid per cent
0-59	33	3	9 1	17	2	11 8	30	6	20 0	13	4	30 8	2	2	100 0
60-69	41	5	12 2	44	14	31 8	87	24	27 6	24	9	37 5	8	5	62 5
70-79	13	4	30 6	24	9	37 5	120	58	48 3	41	28	68 3	20	14	70 0
80-89	16	5	31 3	12	5	41 7	40	25	62 5	12	8	66 7	12	10	83 3
Total	103	17	1[illegible] 5	97	30	30 9	[illegible]	113	40 8	90	49	54 4	42	31	73 8
Age corrected frequencies			20 0			33 4			37 5			50 0			59 0

Table 5

Incidence of fibrillopathy in glaucomatous patients with optic nerve damage

Age Years	Mass screening			Out patients			In patients			Glauc operations		
	Total	Fibr incid		Total	Fibr incid		Total	Fibr incid		Total	Fibr incid	
	No pat	No pat	per cent	No pat	No pat	per cent	No pat	No pat	per cent	No pat	No pat	per cent
50–59	6	1		7	2		17	6		10	4	
60–69	11	1		26	11		52	19		17	9	
70–79	2	1		18	7		95	48		35	26	
80–89	6	1		8	5		35	25		11	8	
Total	25	4	16 0	59	25	42 4	199	98	49 2	73	47	64 4

Table 6

Incidence of fibrillopathy in glaucomatous patients without optic nerve damage

Age Years	Mass screening Total No pat	Mass screening Fibr incid No pat.	Mass screening Fibr incid per cent	Out patients Total No pat	Out patients Fibr incid. No pat	Out patients Fibr incid. per cent	In patients Total No pat	In patients Fibr incid No pat	In patients Fibr incid per cent	Glauc operations Total No pat	Glauc operations Fibr incid No pat	Glauc operations Fibr incid per cent
50–59	27	2		10	0		12	0		3	0	
60–69	9	4		17	3		34	5		7	0	
70–79	11	3		6	2		2	8		4	0	
80–89	10	4		3	0		3	0		0	0	
Total	77	13	16.9	36	5	13.9	71	13	18.3	14	0	–

fibrillopathy between the different groups The incidence was lowest in the mass screening group (16 5 per cent) markedly higher in the out patient group (30 9 per cent) and even higher in the in patient group (40 8 per cent) The dif ference between these groups cannot have arisen by chance (P < 0 0005) The two subgroups of in patients had a still higher frequency The patients operated on for glaucoma showed a frequency of 54 4 per cent while the highest inci dence was recorded among patients with absolute or nearly absolute glaucoma of one eye (73 8 per cent)

The frequency thus increased from group to group in the same order as the increase in the average severity of the glaucoma Table 4 also shows the frequency after correction has been made for uneven age distribution in the different patient groups The variation between different groups has been evened out somewhat but is still very marked The basis for this correction was the frequency among the total number of examined glaucoma patients

Tables 5 and 6 show the frequency of fibrillopathy among patients with and without optic nerve damage in one or both eyes The patients with optic nerve damage (table 5) demonstrated clearly the same increasing sequence in the dif ferent groups in the same order as has been described above The differences shown between the mass screening out patient and in patient groups have not arisen by chance (P = 0 005)

Patients with no optic nerve damage (table 6) showed an almost identical frequency in the different patient groups (P = 0 80)

The frequency of fibrillopathy in the mass screening group of patients was almost the same in patients with and without optic nerve damage (P = 0 90) Markedly higher frequencies were however demonstrated in patients with optic nerve damage than in patients without optic nerve damage in the out patient group (P < 0 01) and in the in patient group (P < 0 0005)

Finally table 7 shows the frequency of fibrillopathy in the different patient groups after correction has been made both for age and for the severity of the glaucoma The standard for the correction has been the frequency among pa tients respectively with and without optic nerve damage in the total material

Table 7

Frequency of fibrillopathy in different groups of glaucomatous patients when correction has been made for age and severity of glaucoma

	Mass screening	Out patients	In patients	Glauc operations
Percentage	26 1	33 2	35 3	44 8

The corrected frequencies still show some variation from group to group but the differences are appreciably smaller than in the observed frequencies

Discussion

The results of this study indicate that the incidence of fibrillopathy among patients with open angle glaucoma is the same in both sexes

Age on the other hand appears to be of great significance The frequency of this condition appears to rise steeply with increasing age In a number of earlier published papers no precise indication of the age distribution is given A comparative analysis of these studies is therefore not possible

In the present investigation the observed frequencies and incidences have been subjected to mathematical and systematic correction in order to allow for uneven age distribution The corrected results show only slight difference from the observed results The differences in the frequencies must therefore have another explanation

The severity of glaucoma seems to have a very definite relation to the incidence of fibrillopathia epitheliocapsularis In the present study it has been shown that the incidence of fibrillopathy in patients with optic nerve damage was about three times as high as in patients with normal discs and visual fields This fact will also be reflected in different patient groups examined It is evident that the proportion of patients with severe glaucoma increased according to their mode of selection in this order mass screening patients out patients in patients patients operated on for glaucoma and patients with absolute or nearly absolute glaucoma In this same order an increasing incidence of fibrillopathy was demonstrated from 16 5 per cent in the mass screening group to 73 8 per cent in the absolute or nearly absolute glaucoma group (Table 4) The results concur well with the assumption that capsular glaucoma seems to be a more serious form of glaucoma than simple glaucoma This assumption will be elaborated in another work by the present author (Aasved)

The observed increase in the frequency is markedly reduced but still present after making correction for both age and the severity of glaucoma This may indicate that other still unknown factors might play a role Some of the difference may however also be due to a somewhat rough classification of the patients both with regard to age groups and to the clinical severity of the glaucoma

The age distribution shows that there were relatively more persons in the younger age classes in the mass screening group and to a somewhat lesser degree also in the out patient group than in the in patient group It is therefore possible that there was a correspondingly lower average age in each 10 year

group in the above mentioned sequence although this would hardly influence the total frequency appreciably

It is more probable that the roughness of the classification of the severity of the glaucoma is more important

The increase of the frequency from group to group appears to be confined to patients with optic nerve damage while the incidence among patients without optic nerve damage seems to be the same in the different groups Thus even if an examination comprises only patients with optic nerve damage one might find great variations in the incidence of fibrillopathy In such a group however one would also expect great variation in the severity ranging from a barely noticeable excavation of the optic disc or a small Bjerrum scotoma to an absolute glaucoma One might postulate that even among patients with optic nerve damage the severity of glaucoma increases in this order mass screening patients out patients in patients patients operated on for glaucoma patients with absolute glaucoma It may be mentioned that there was only one patient with absolute glaucoma in the mass screening group and two in the out patient group whereas 42 patients with absolute or nearly absolute glaucoma were found in the in patient group the latter representing a considerably higher frequency than the two former groups

The important fact in this context is that the highest frequency of fibrillopathy was found among patients with absolute or nearly absolute glaucoma

Patient groups with a lighter degree of optic nerve damage will therefore be expected to show a lower incidence of fibrillopathy than patient groups with advanced optic nerve damage

The assumption discussed above may to some extent explain why there still is a difference in the frequency of fibrillopathy between the different groups of patients even after corrections have been made for age and severity of glaucoma

This survey shows beyond doubt that different patient groups even from the same geographical area may show great variations in the frequency of fibrillopathy It seems to be of the greatest importance that the frequency is much higher in patient groups with severe cases of glaucoma than in groups with lighter cases

It is not unreasonable to presume that variation in the age distribution and especially in varying severity of the glaucoma may explain in whole or in part the great variation in the reported frequencies in earlier studies

The frequency found in this study in patients from the mass screening and from the out patient groups concurs well with a number of former studies of fairly comparable groups both in Norway (*Bertelsen et al* 1965) and in other countries (*Garrow* 1938 *Wilson* 1953 *Kaivonen* 1961 *Gillies* 1962 *Ladekarl* 1965 *Horven I* 1966 and *Sood* 1968)

However the frequencies not only in these groups but in the total material

are considerably lower than those reported in a number of former works from Norway (*Horven E* 1935 *Holst* 1941 *Thomassen* 1949 *Petersen* 1958) who quote frequencies from 77 per cent to 93 per cent The frequencies from these latter studies form the main foundations for the general view that the frequency of fibrillopathy among glaucoma patients is particularly high in Norway Two of the materials permit further analyses (*Horven E* 1935) In one of them all 150 patients had been operated on for glaucoma The other patient group con sisted of 43 patients of whom at any rate 41 had glaucomatous optic nerve da mage in one or both eyes and it also included 26 patients with absolute or nearly absolute glaucoma Both these materials were thus made up of advanced and serious cases of glaucoma In this present study the group of patients operated on for glaucoma and the group of patients with absolute or nearly absolute glaucoma consists of cases with approximately the same severity As expected the fibrillopathy frequencies found in these two groups were of approximately the same magnitude It seems probable that other materials (*Holst* 1947 *Thomassen* 1949 and *Petersen* 1958) which originate from the same University Department as the one reported by Horven also consist mainly of s rious cases of glaucoma This University Department was at that time the only one in Norway which accepted patients from the whole country and ophthalmologists from a large area may have sent their most severe cases of glaucoma to this hospital while treating the more easily controlled cases themselves These studies also took place in a period when it was uncommon to perform tonometry as a routine measure on every eye patient above a certain age These factors combined with a great general interest for fibrillopathy among Norwegian ophthalmologists may have resulted in especially selected glaucoma materials with an over weight of capsular glaucoma

It is difficult to analyse earlier glaucoma materials in which an especially low fibrillopathy frequency has been demonstrated Several different factor may have played a part for instance the method of collection the size of the examined population the conditions of examination the experience of the examiner and especially his interest in the condition Thus the latest material from the U S shows a frequency which agrees well with the findings of the present study (*Horven I* 1966) Earlier surveys however showed very low frequencies (*Irvine* 1940 *Cradle & Sugar* 1940 and 1941 *Lemoine* 1950)

Earlier materials also indicated a very low frequency among glaucoma pa tients in England (*Thomassen* 1949 *Jones* 195 *Hollows & Graham* 1966) and in Germany (*Blaickner* 1937 *Leydhecker* 1960)

The present author had the opportunity to see 103 patients with open angle glaucoma at the out patients clinic of Birmingham and Midland Eye Hospital Most of the patients examined had miotic pupils and examination condition did not permit dilatation Fibrillopathy was found in 13 of these patients (12 5 per cent) The present author also examined 11 glaucoma patients during a mass

screening session in Bonn Germany Two of these were found to have fibrillopathy A recent German study of 200 glaucomatous eyes revealed 23 eyes with fibrillopathy *(Barkhoff 1969)* These findings indicate that the fibrillopathy frequency in England and Germany is considerably higher than earlier indicated

The total frequency of fibrillopathy among all patients with open angle glaucoma examined in this present study was 32 9 per cent. This figure must also be considered to be somewhat higher than one would expect in the glaucoma population of Norway The eye department in Bergen accepts glaucoma patients from about 10 eye specialist practices in Western Norway It is usually the cases of open angle glaucoma which fail to respond satisfactorily to ordinary medication in the course of ambulant treatment that are referred to the department It must therefore be assumed that his material also has an overweight of difficult and severe cases This fact will as shown above result in a higher fibrillopathy frequency On the other hand the frequency found in the mass screening group is a minimum figure It is therefore a natural assumption that the true frequency of fibrillopathy among patients with open angle glaucoma in Norway is in the range of 20–30 per cent and thus probably not higher than in other countries

In conclusion it may be said that the frequency of fibrillopathy found in a glaucoma material will depend to a very great degree on the composition of the material with regard to age and especially to the severity of the glaucoma

Summary

A total of 444 patients with open angle glaucoma has been examined It has been found that the frequency of fibrillopathia epitheliocapsularis (the so called senile exfoliation or pseudoexfoliation) depends to a considerable degree on the patient groups examined The sex of the patients appears to be without significance but the frequency increases with increasing age

The most important factor however appears to be the severity of glaucoma The frequency was considerable higher among patients with optic nerve damage than among patients with normal optic discs and visual fields Different patient groups collected from the same geographical area but with varying degrees of severity showed an increasing frequency of fibrillopathy in the same sequence as the severity

The recorded frequencies in the different groups were as follows Patients found on mass screening 16 5 per cent out patients 30 9 per cent in patients 40 8 per cent patients operated on for glaucoma 54 4 per cent and patients with absolute or nearly absolute glaucoma 73 8 per cent These findings seems to

concur well with the clinical experience that capsular glaucoma is a more serious condition than ordinary simple glaucoma

Among patients with open angle glaucoma in Norway as a whole it is assumed that the frequency of fibrillopathy is in the range of 20–30 per cent and thus probably not higher than in other countries

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From the Ophthalmic Department (Head Professor H Forsius) of the University Hospital Oulu Finland

DARK ADAPTATION IN DICHROMATS AND ANOMALOUS TRICHROMATS

BY

ANNI KARMA

Dark adaptation involves a rapid cone adaptation followed by a slower rod adaptation The photochemical reactions and nerve mechanisms in rod adaptation are incompletely known and even less is known about cone adaptation If the dark adaptation of a healthy subject is plotted on a semilogarithmic scale the curve takes a given shape This shape is governed by the retinal region measured the insensity duration and wave length of the preadaptation light and the duration and wave length of the light stimulus

Denden (1964 1966 and 1967) (1 2 3) reported on studies of dichromats and anomalous trichromats and their dark adaptation to white light The results varied and no conclusive differences compared with the normal adaptation curves emerged

The purpose of the present study was to discover whether this method was capable of bringing to light differences in the adaptation curves of dichromats and anomalous trichromats compared with normal curves

Material and Methods

The series consisted of 50 national servicemen with defective color vision and 14 with normal color vision, all aged about 20 years The *Bostrom Kugelberg* (Kifa 1944) and II *Bostrom* (Kifa 1950) pseudo isochromatic tables were used to detect color defectives

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After the first minute readings were taken every half minute for 15 minutes and then approximately every 2 5 minutes until the end The brightness of the test plate was increased gradually by about 0 1 logarithmic units at a time until the subject discerned the stripes which he indicated by turning the stripes in a horizontal position

The readings were automatically recorded on a semi logarithmic graph The abscissa showed the time in minutes and the ordinate the logarithm of the intensity of threshold light ($log_{10}\mu lux$) All dark adaptation tests were carried out in identical constant conditions at the same time of day between 18 00 and 21 00 hours The weather of the relevant day was recorded

The statistical treatment of the adaptation curves obtained was effected group by group During the first 15 minutes of dark adaptation the numerical values of the points of the curves were recorded for every half minute and after that for every 2 5 minutes The last point where the curves coincided was at 37 5 minutes

A mean value curve for each group the deviation of each point and the standard error of the mean value were calculated by computer

Mean value formula

$$\bar{x} = \sum_{i=1}^{n} \frac{x}{n}$$

in which

$\bar{x}$ = arithmetic mean value
n = number of numerical values
x = individual numerical value
Σ = the sum of individual numerical values
i = the course from 1 to n

Formula of standard deviation

$$\delta = \sqrt{\frac{\Sigma(x - \bar{x})^2}{n - 1}}$$

Formula of the standard error of mean value

$$\delta_{\bar{x}} = \frac{\delta}{\sqrt{n}}$$

After 15 minutes of dark adaptation the threshold values of both eyes were recorded separately The statistical treatment however included the threshold values of only the right eye since the terminal sections of all curves were found to be congruent

Results

In all mean value curves the threshold value fell sharply during the first minute Subsequently the curves showed a gentler slope After 15 minutes of adap

The "Boström positive" men were examined with the Nagel anomaloscope and with the Farnsworth D_{15} test Color vision anomalies were classified on the basis of the results of anomaloscopy and Farnsworth D_{15} test as follows

Dichromat (D_1 or P_1) In anomaloscopy the testee accepted an equation at both extreme ends of the color mixture scale himself handling nothing else but the yellow control knob His Farnsworth D_{15} test zigzagged (4)

Markedly anomalous trichromat (D_2 or P_2) In anomaloscopy the testee did not accept the equation of the normal observer but chose instead an equation of his own The Farnsworth D_{15} test zigzagged

So called "extreme deuteranomals" were also among this group They under improper tuning accepted a match at or very near the extreme green position of the color mixture knob

Slightly anomalous trichromat (D_3 or P_3) In anomaloscopy the testee did not accept the equation of the normal observed but chose instead an equation of his own The Farnsworth D_{15} test was normal (4)

The distribution of the color vision defects was 5 subjects with deuteranopia i e 10 per cent 33 with marked deuteranomaly i e 66 per cent 7 with slight deuteranomaly i e 14 per cent 3 with protanopia i e 6 per cent and 2 with marked protanomaly i e 4 per cent There were no subjects with slight protanomaly i e 0 per cent The distribution corresponded to the assumed Scandinavian values (5)

The normal subjects also underwent all these color vision examinations In addition the vision and ocular fundi of all subjects were examined Six of them had myopia ranging from –2 to –6 D All the others could without spectacles see better than 1 0 on Snellen s E table Two of those examined one of group D_1 and the other of group D_2 had unusually light coloured ocular fundi which however could be classified as normal The other fundi gave no ophthalmoscopically abnormal findings

The examination was carried out using the *Goldmann Weekers* (Haag Streit) adaptometer without spectacles and with undilated pupils Five minutes (± 15 sec) of light adaptation with about 2900 asb were followed by about 35 minutes of dark adaptation The first 15 minutes of the test were binocular and later monocular the subject covering first his left and then his right eye with the palm of the hand Throughout the examination the subject was repeatedly requested to fix his eye(s) on the red fixation point 11° above the test plate The maximum brightness of the field of stimuli was 6 lux The test plate consisted of a striped figure with 100 per cent contrasts

Five readings were taken during the first minute after light adaptation Every effort was made to obtain the first reading as soon as possible after the dark adaptation had begun and it was obtained after an average of 5 seconds During the first minute the subject was requested to say when he began to distinguish the stripes

After the first minute readings were taken every half minute for 15 minutes and then approximately every 2 5 minutes until the end The brightness of the test plate was increased gradually by about 0 1 logarithmic units at a time until the subject discerned the stripes which he indicated by turning the stripes in a horizontal position

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Results

In all mean value curves the threshold value fell sharply during the first minute Subsequently the curves showed a gentler slope After 15 minutes of adap

tation all mean value curves had almost reached their final threshold value level and fell by a maximum of 0 2 logarithmic units until the final value at 37 5 minutes

The sector of the mean value curve representing the cone rod shift fell between 6 and 9 minutes, differently in different groups No sector of this type could be discerned in the mean value curve of the protanopes

In the present study the rod adaptation of the protanopes proved to be considerably below the normal level as did the cone adaptation of the deuteranopes The mean value curves of the other groups showed no remarkable differences from the normal mean value curve

During the first 15 minutes the initial sector of the individual curves appeared more or less zigzag It was by no means always possible to distinguish any sector that could be interpreted as a cone rod shift

In the present study no correlation could be noted between the brightness of the day the time of the cone rod shift and the final threshold value Nor did refraction defects seem to affect the shape of the curve The low degree of retinal pigmentation in the two subjects and the shape of the adaptation curve were not correlated

Normals (14) (fig 1)

After the sharp fall of the threshold value during the first minute the curve

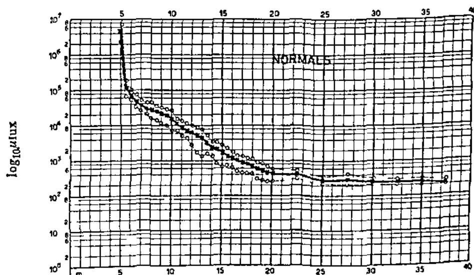


Fig 1

Mean value curve and standard deviation of 14 normal subjects aged about twenty years

declines smoothly After 15 minutes of adaptation the threshold value falls al most to its final level The cone rod shift or *0 4 logarithmic units occurs at 6–7* minutes The deviation is small

Deuteranopes (5) D_I (fig 2)

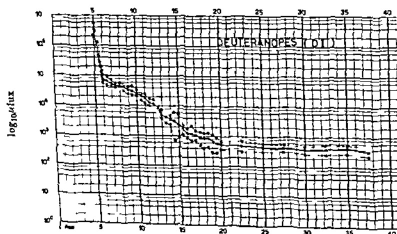
After the sharp fall of the threshold value during the first minute the mean value curve over the cone sector remains at a level higher than that of the nor mal subjects The scotopic sector is as long as that of the normal curve The mean value curve is smooth and the deviation over the cone sector is below and over the rod sector equal to that of the normal curve The cone rod shift 0 5 logarithmic units occurs at 7–8 min

Deuteranomals (33) D_2 (fig 3)

The course of the mean value curve corresponded to the normal curve The cone rod shift 0 5 logarithmic units occurs at 7–8 min The deviation of the cone sector equals that of the normal curve while over the rod sector it is very much greater *almost 1 5 logarithmic units*

Deuteranomals (7) D_3 (fig 4)

The course of the rod sector of the curve is less regular than that of the normal



Fig

Mean value curve and standard deviation of 5 deuteranopes aged about twenty years

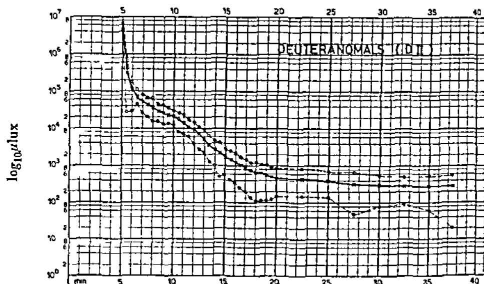


Fig 3
Mean value curve and standard deviation of 33 subjects with marked deuteranomaly aged about twenty years

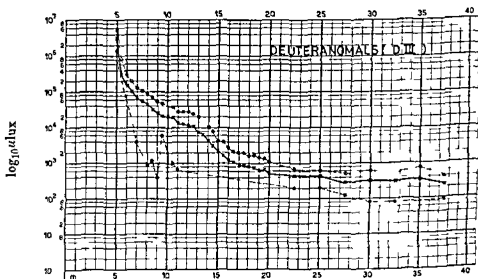


Fig 4
Mean value curve and standard deviation of 7 subjects with slight deuteranomaly aged about twenty years

curve and the deviation is large The sector to be interpreted as the cone rod shift falls at 8–9 min The rod sector ends at a level equal to that of the normal curve

Protanopes (3) P_I (fig 5)

The course of the cone sector is irregular There is no sector which could be considered the cone rod shift The scotopic sector of the mean value curve is distinctly inferior to that in the normal curve due to the below normal rod adaptation of one protanopia curve This individual result was checked and confirmed by a repeated examination The two other protanopia curves did not appreciably differ from the normal curve

Protanomals (2) P_a (fig 6)

The cone sector of the mean value curve resembles a plateau A cone rod shift 0 6 *logarithmic units falls at 7.5–8.5 min* and *another* 0 4 logarithmic units at 14–15 *min* is seen in the range of the rod function The rod sector ends at a level corresponding to the normal

Comparison of the most important points of the mean value curves of the groups can be facilitated by means of a table (table 1)

Discussion

The mechanisms of dark adaptation are incompletely known The photochemical reactions of the rods resynthesis of rhodopsin however are probably re

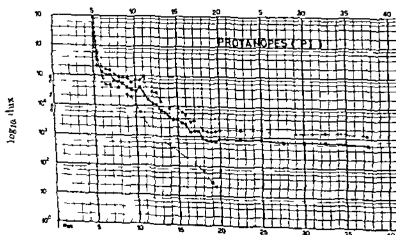


Fig 5

Mean value curve and standard deviation of 3 protanopes aged about twenty years

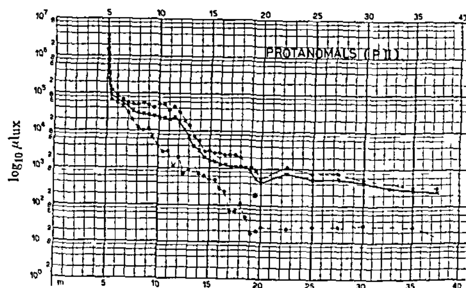


Fig 6

Mean value curve and standard deviation of 2 subjects with marked protanomaly aged about twenty years

Table 1

Comparison of the most important points of the mean value curves of the groups

Group	Size of group	△	Tα	α	Tβ	β	k
Normal	14	1 7	6–7	0 4	–	–	± 0
D_1	5	1 7	7–8	0 5	–	–	— 0 1
D_2	33	1 4	7–8	0 5	–	–	— 0 0[illegible]
D_3	7	1 2	8–9	0 4	–	–	— 0 0[illegible]
P_1	3	1 5	–	–	–	–	— 0 40
P	2	1 6	7 5–8 5	0 6	14–15	0 4	— 0 0[illegible]

△ Fall in the threshold value within the first minute (logarithmic units μlux)

Tα Time of the cone rod shift minutes after the beginning of adaptation

α Extent of the cone rod shift in one minute (logarithmic units μlux)

Tβ Time of the second shift minutes after the beginning of adaptation

β Extent of the second shift in one minute (logarithmic units μlux)

k Difference between the final threshold value and that of the normal mean value curve (logarithmic units μlux)

The minus sign indicate a subnormal final threshold value

sponsible for the photochemical role of the rods Similar reactions are assumed to take place in cone adaptation although no cone pigment similar to rhodopsin has been discovered in man (*Rushton* 1961) (6)

Rushton (7) also showed that color vision was based on the presence of photosensitive pigments He demonstrated that there are two different pig ments one sensitive to red and the other sensitive to green Rushton found furthermore that one of these pigments is absent in dichromats the red sensitive in the protanope and the green sensitive in the deuteranope A certain photo chemical difference in the dichromats might affect the dark adaptation

The present study used the same method as Denden in his studies (1 2 3) A difference was however that in the present study the early part of the adap tation was binocular whereas Denden used monocular adaptation The binocu lar method of the study tends to smooth the curves somewhat (8)

In the adaptation curves of deuteranopes and protanopes Denden (1) has found one cone rod shift at 6 min but this was later followed by another for deuteranopes at 11 min and for protanopes at 13 min These latter coincided with the rod function range

The present study failed to confirm this finding Only the subjects with marked protanomaly showed a second shift in the rod function range

Further Denden has found in his studies that deuteranopes and protanopes had a better rod adaptation than the normal subjects (2 3) The present results do not confirm this finding The cone function of deuteranopes in the present study was found to remain below the normal level whereas the rod function did not appreciably differ from the normal On the other hand the rod adap tation of the protanopes was found to be distinctly below the normal level

No definite conclusions can be drawn concerning the differences in the pre sent results within the deuteranopic and protanopic groups owing to their small size

For 33 eyes with marked deuteranomaly the standard deviation of mean alue curve in the scotopic sector considerably exceeded that for normal eyes It suggests that matching range of deuteranomaly has its influence on the rod sector of dark adaptation However no logical correlations could be found when comparing matching range of a particular deuteranomaly and dark adap tation rate over the rod sector

Summary

The mean value curves of the dark adaptation of 50 national servicemen aged about ᵒ0 and with color anomalies were examined and compared with the mean value curve of normal subjects

The series comprised 14 subjects with normal color vision 5 with deuteranopia 33 with marked deuteranomaly 7 with slight deuteranomaly 3 with protanopia and 2 with marked protanomaly

The cone sector of those with deuteranopia was smooth showed a narrow range of deviation and was distinctly inferior to that in the normal curves In the other groups the cone sector did not appreciably differ from that of the curve for the normal subjects

The rod sector ended at a level corresponding to the normal in all curves but those for the protanopes In their mean value curve the rod sector was distinctly inferior to that in the curve for the normal subjects

The initial sectors of the individual curves were often irregular and the cone rod shift could by no means always be discerned

The scotopic sector in all groups of color defectives showed a standard deviation of the mean value curve distinctly exceeding that for normal eyes

The present results suggest that the type and degree of color vision anomaly has its influence unexplored todate on the course of dark adaptation in the sector of both cone and rod function

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From the University Eye Hospital Oulu Finland
(Head Professor Henrik Forsius)

A CASE OF CAVERNOUS HAEMANGIOMA OF THE RETINA

BY

ULF KRAUSE M D

Angiomatous tumours of the retina are relatively rare and they are often a diagnostic problem The main types are briefly described below

In angiomatosis of the retina (Lindau von Hippel s disease) a cherry red or whitish globular tumour is seen consisting of hyperplastic capillaries and proliferated glial tissue The tumour which is a congenital mesodermal malformation (*Reese* 1963) forms an anastomosis between widened afferent and efferent wessels In the late stages transudate haemorrhages and retinal detachment are observed round the tumour and the clinical picture may resemble that of Coats syndrome The changes may be multiple and bilateral (*Sæbø* 1952)

According to *Reese* (1963) in Coats syndrome the typical feature is a local globular dark or greenish brown retinal detachment over which multiple small teleangiectases are seen As a rule the disease affects young children The process is usually but not invariably progressive *Duke Elder* (1967) considered exudative and haemorrhagic conditions due to leakage from impaired blood vessels as belonging to this symptom complex When the condition is progressive the bulb is filled by white (yellowish) prominent masses of connective tissue partly covering the retinal vessels Cholesterol crystals and haemorrhages are sometimes seen and all types of vascular abnormalities occur The histological picture and fluorescein angiographic findings are typical (*Wessing* 1968) Multiple retinal aneurysms of Leber were interpreted by *Reese* (1963) as a precursor to Coats syndrome

In cavernous retinal haemangiomas the ophthalmoscopic picture shows a relatively well demarcated tumour with reddish or purplish spherules somewhat

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Fig 1 A

Tumour in the left eye of a 37 year old woman Dark spherules are seen peripherally while the central portions are white Temporally above an abnormal blood vessel runs toward an apparently normal retina



Fig 1 B

Nasal part of the tumour with raspberry like reddish prominences

like a raspberry alternating with larger light areas (*Niccol* & *Moore* 1934 *Scheyhing* 1937 *Piper* 1954 *Thiel* 1963) The surrounding retinal vessels seem

to be normal *Garrow & Loewenstein* (1943) described a histologically diagnosed choroidal cavernous haemangioma with a stilated process situated within the retina *Reese* (1963) however doubted the occurence of cavernous retinal haemangiomas

Racemose haemangiomas are congenital vascular anomalies affecting the retina as a whole or in part The presence of large and tortuous vessels of non descript type are the dominant feature (*Krug & Samuels* 1932 *Wyburn Mason* 1943 *Thorkilgaard* 1963) Racemose haemangiomas often occur in conjunction with vascular midbrain lesions causing hemianopsia or epilepsy and they are almost invariably associated with symptoms of intellectual and mental disturbances (*Wyburn Mason* 1943)

Choroidal haemangiomas are usually seen near the papilla but the whole choroid may be involved (*Jones & Cleasby* 1959) As a rule the tumour is light yellow or grey the surface is smooth and covered by an epichoroidal membrane showing a tendency towards ossification (*Stoewer* 1908 *Gareis* 1956 *Jones & Cleasby* 1959) Dilated retinal and choroidal vessels may be seen nearby (*Jones*



Angiogram 1

Nasal portion of the tumour in the late arterial phase Three anomalous vessels are seen (arrows) Anastomoses are possibly present between the vessels of the tumour and retina Early filling of vascular ampoules (8 sec.)



Fig 1 A
Tumour in the left eye of a 37 year old woman Dark spherules are seen peripherally while the central portions are white Temporally above an abnormal blood vessel runs toward an apparently normal retina



Fig 1 B
Nasal part of the tumour with raspberry like reddish prominences

like a raspberry alternating with larger light areas (*Niccol* & *Moore* 1934 *Scheyling* 1937 *Piper* 1954 *Thiel* 1963) The surrounding retinal vessels seem

Right eye Vision 1 2 Refraction + 1 0 D Aqueous flare − The cornea iris lens vitreous and ocular fundus were normal Ocular tension was 16

Left eye Vision 0 1 Aqueous flare − The cornea iris and lens were normal The vitreous was clear In the ocular fundus a 4 D promient well demarcated tumour was observed, ranging from the area between the optic disc and macula and extending temporally as far as the periphery (Fig 1) Normal retinal blood vessels ran to the tumour and in part over it Both the efferent and afferent vessels were normal Temporally above the tumour an abnormal blood vessel was seen which sent out branches over an apparently normal retina without anastomosing with other retinal vessels The central portions of the tumour were light whitish resembling cicatricial tissue Nasally in particular the periphery of the tumour was raspberry like with blood stained pigmented light and grapelike prominences Below a relatively large coherent haemorrhage was seen. No exudate or crystals were observed Biomicroscopy showed a low retinal detachment nasally The creased retina merged into the superficial layer of the tumour Cranially of the tumour a local detachment of vitreous was seen

The visual field showed a defect corresponding to the extension of the tumour An X ray of the left orbit showed no intracranial calcifications and no local ossification in the left eye The patient had no facial angiomas

Fluorescein angiography showed more or less normal retinal vessels running towards the area of the tumour No definite anastomoses between the dilated vascular globule



Angiogram 3

Fluorescence is maximal and new ampoules still appear There is no fluorescence in the narrower blood vessels Background fluorescence is increasing (11 min. / sec.)

& *Cleasby* 1959) and the tumour may extend intraretinally (*Garrow & Loewenstein* 1943) The diagnosis is a problem, as a rule malignant melanoma is suspected (*Mulock Houwer* 1925 *Jaensch* 1932 *Brons* 1936 *Rosen* 1950 *Dufour* 1954 and others) About 50 per cent of the patients also show facial angiomas (Sturge-Weber syndrome) In those cases the diagnosis is more readily made

Case report

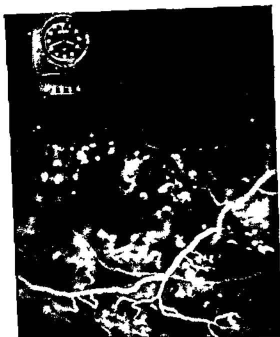
A 37 year old woman was admitted to the Eye Clinic in September 1968 under a diagnosis of Haemangioma retinae? o sin Strabismus divergens o sin She had a history of having hurt the left eye when falling as a child After this a divergent squint was observed but the patient was not seen by an ophthalmologist until 1955 Vision on the left eye was then 0 2 and temporally below and extending towards the optic disc a tumour exhibiting superficial haemorrhages was seen A diagnosis of Haemangioma chorioidae (?) was made In 1961 1962 and 1968 the patient was treated at a mental hospital under a diagnosis of schizophrenia

The following observations were made on admission to the Eye Clinic



Angiogram 2

The fluorescence is intravascular new dilatations are seen Filling of the globules proceeds slowly from one pole (1 min 47 sec)



Angio ram 5
Upper temporal portion of the tumour Filling is observed in some ampoules and their fluorescence is stronger than that of the anomalous vessel (1 min)

after °0 minutes when angiography was interrupted Enucleation was suggested because of the patient s fear of malignancy but she refused Two months later she permitted suicide The left eye was not removed post mortem for histological investigation.

Discussion

The tumour in the left eye of this patient was first observed in 19ɔ5 when it obviously was already about the same size as in 1968 The fact that the process was only slowly or not at all progressive argues in favour of the assumption that the tumour was benign and that the divergent squint shown by the patient since she was a child may have been due to a congenital anomaly affecting the macular area The slight progress noted during eight months parallels the observations made in a clinically similar case described by *Scheyhing* (1937) which he considered as a congenital malformation Similar conclusions were drawn by *Niccol & Moore* (1934) in a case described by them

The benign tumour reported in the foregoing showed no globular arteriove

and normal retinal vessels were seen Teleangiectases were filled from one pole (Angiogram 1) Some large abnormal vascular sloops were filled in the arterial stage The fluorescence was strictly intravascular throughout the time of observation (Angiogram 2) An increasing number of new ampoules appeared While the fluorescence in previously partially filled ampules still increased the fluorescence of other vascular elements decreased and the process reached its maximum after slightly more than 11 minutes (Angiogram 3) Circulation was very slow Almost the same electron microph like picture was seen after 28 minutes (Angiogram 4) The background fluorescence had increased At this stage angiography was interrupted

Separate angiography of the upper temporal portion of the tumour showed a slow increase of the fluorescence of the ampoules" during the observation time of slightly more than 10 minutes (Angiograms 5 and 6) The large anomalous vessel of nondescript type sending branches towards a normal retina showed a weaker fluorescence throughout than the teleangiectases

A diagnosis of haemangioma of the retina was made Enucleation was not suggested.

At follow up eight months later vision on the left eye was the same and no changes in the appearance or extension of the tumour were noted

Repeated fluorescein angiography of the same areas showed a shadow (pigment? thrombosis?) in a previously homogenously fluorescent area (Angiogram 7) Just as previously a very slow circulation with definite fluorescence was observed in the tumour



Angiogram 4

Strong fluorescence after 28 min There is hardly any change as compared to the situation 17 min earlier



Angiogram 7
The situation at follow up after 8 months corresponds to the earlier findings Arrow A dark shadow not previously observed

vestigated (*Niccol & Moore*) *Reese* (1963) consid red this type of tumour as very rare or not occuring at all

Choroidal haemangiomas may extend intraretinally (*Garrow & Loewenstein* 1943) but as a rule the overlying retina is ophthalmoscopically normal An ossified epichoroidal membrane is sometimes seen on X rays but in the present case no such membrane was observed As already mentioned choroidal haemangiomas have also been included among the symptoms of the not well defined Sturge Weber syndrome *Smith et al* (1963) described the angographic findings in choroidal haemangioma The present patient showed no features in common with the case reported by them Finally it is difficult to understand why a choroidal haemangioma would give rise to nondescript vessels outside the area of the tumour in an apparently normal retina

Angiography showed that circulation in the tumour was very slow At an early stage most of the superficially situated spherules looked as if they were thrombosed but after a sufficiently long observation time the teleangiectases were gradually filled by homogenously fluorescent blood



Angiogram 6

The same area as in angiogram 5 New teleangiectases are observed and the background fluorescence is stronger than before There is no leakage from abnormal vessels (10 min 37 sec)

nous anastomoses and the retinal blood vessels were not dilated Hence Lindau von Hippel s disease must be excluded A diagnosis of Coats syndrome with teleangiectases haemorrhages white masses and retinal detachment can be eliminated since the angiographic finding typical of this syndrome (*Wessing* 1968) consisting of newly formed capillaries extravascular fluorescence etc was lacking

In racemose haemangiomas of the retina mental disturbances are common just as in Sturge Weber disease The present patient was schizophrenic but she lacked facial angiomas Moreover an X ray of the skull showed no calcifications and no calcifications were observed at autopsy Since the ophthalmoscopic finding also differed from those described in the literature in racemose haemangiomas (*Krug* & *Samuels* 1932 *Wyburn Mason* 1943 *Reese* 1963 *Thorkilgaard* 1963 and others) this tumour can be ruled but as a diagnostic alternative

Thus of the benign retinal tumours only cavernous haemangioma remains Clinically similar cases have been described (*Niccol* & *Moore* 1934 *Scheyhing* 1937 *Piper* 1954 *Thiel* 1963 *Frenkel* & *Russe* 1967) and also histologically in

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Attempts at establishing the retinal or choroidal origin of the tumour by the aid of angiography were resultless

Summary

An unusual type of angiomatous tumour in the left eye of a 37 year old woman clinically diagnosed as cavernous haemangioma of the retina is described

Angiography showed a very slow circulation in the area involved After eight months a very slight progress of the tumous was observed

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(Fig 1) The lid movements occuring in horizontal gaze were examined with the help of an arc perimeter The patient s chin was placed on the rest of the perimeter with the arc placed horizontally The subject was asked to look into the center of the instrument and to shift his gaze maximally to each side of the arc The width of the palpebral fissure was measured between the above described ink marks with the help of a caliper The measurements were performed in the primary position and during maximal horizontal movements to the right and to the left for each eye separately

The upper eyelid was considered to be significantly elevated in abduction or adduction when the displacement of the lid was of 1 mm or more beyond that of the primary position

In one normal subject electromyography of the Levator palpebrae was performed with the eye in the primary position and during maximal abduction

Results

Table I summerizes these findings Of the 133 subjects with normal eye motility elevation of the upper eyelid of 1 to 2 mm occured during abduction bilateraly in 56 patients and unilateraly in 9 In adduction this phenomenon occured bilateraly in 15 cases and unilateraly in 6 In 17 cases elevation of the eyelid occured in both abduction and adduction This phenomenon was not noted unilateraly

No elevation of the lid during abduction or adduction was observed in 30 cases (22%)

It is apparent that the subjects with normal eye motility presented 4 main types of eyelid behaviour during abduction or adduction of the eye

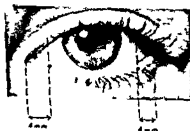


Fig 1
Width of palpebral fissure as measured between preplaced ink marks

Department of Ophthalmology Hadassah Medical Center Jerusalem Israel

SYNKINESIS OF UPPER LID ELEVATION OCCURRING IN HORIZONTAL EYE MOVEMENTS

BY

U TICHO M D

The elevation of the upper eyelid occuring in horizontal eye movements has been reported as a rarity by several authors (*Browning* 1890 *Pfluger* 1893 *Phillips* 1887 & *Fuchs* 1893) However the phenomenon has been described as occuring frequently in cases suffering from 6th nerve palsy (*Friedenwald* 1896 *Sinclair* 1895) 3rd nerve palsy (*Fuchs* 1893) and Duane s Syndrome (*Duane* 1905)

During routine examination of normal subjects the impression was obtained that the elevation of the upper lid in conjugate horizontal gaze was a rather common phenomenon In the light of this it was decided to further evaluate this movement of the upper lid in normal subjects and in cases affected with abducens paresis and Duane s Syndrome

Material and Methods

One hundred and thirty three consequative subjects with normal eye motility 60 males and 73 females between 5 and 70 years were investigated for this study The subjects were students nurses and medical staff having no eye or obvious neurological or endocrine disease In addition 6 subjects suffering from abducens paresis and 3 with Duane s retraction syndrome were examined

The eyelid margins were marked with ink 4 mm away from each canthus

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Fig 4

Subject with normal eye motility presenting elevation of the upper eyelid during adduction of the right eye



Fig 5

Subject with normal eye motility presenting in both eyes elevation of the upper eyelids during abduction and adduction



Fig 6

Subject with normal eye motility The upper eyelid forms on abtuse angle during its elevation on abduction of the eye ball

The influence of age on the phenomenon described is shown in Table II There are two *interesting* and *apparently contradictory features* Practically all the 17 cases showing the lid elevation on both adduction and abduction were over 30 years and all the 30 cases showing the complete absence of elevation were over 30 years The elevation was not observed in subjects over 50 years of age The phenomenon was observed equally in both sexes

In the 6 cases with 6th nerve palsy a 3 to 5 mm elevation of the upper lid was observed on attempted abduction (Fig 7) In 4 of the cases elevation of 1 to 3 mm found on adduction as well

Three cases suffering from Duane s syndrome presented a 2 to 3 mm elevation of the eyelid on abduction while an adduction a 1 mm depression of the lid was present

In one normal subject an increment of electrical activity of the Levator Palpebrae was found during maximal abduction of the eye ball (Fig 8)

Table I

Elevation of upper eyelid on abduction and adduction in 133 normal subjects.

Number of cases showing Elevation of the eyelid on					
abduction		adduction		both abduction and adduction	
both eyes	one eye	both eyes	one eye	both eyes	one eye
56 (42 %)	9 (7 %)	15 (11 %)	6 (4 %)	17 (14 %)	-

In 30 (22%) subjects no elevation of the lid occured on either abduction or adduction of the eye ball

a Eyelids exhibiting no elevation in either direction (Fig 2)
b Eyelids exhibiting elevation during abduction only (Fig 3)
c Eyelids exhibiting elevation during adduction only (Fig 4)
d Eyelids exhibiting elevation during both abduction and adduction (Fig 5)

While the upper lid was in elevation it was usually observed that the lid margin lost the curved contour and became somewhat angulated in the junction of the inner and medial thirds (Fig 6)



Fig 2

Subject with normal eye motility presenting no upper eyelid elevation on either abduction or adduction



Fig 3

Subject with normal eye motility presenting elevation of upper eye lid during abduction of the left eye



Fig 4

Subject with normal eye motility presenting elevation of the upper eyelid during adduction of the right eye



Fig 5

Subject with normal eye motility presenting in both eyes elevation of the upper eyelids during abduction and adduction.



Fig 6

Subject with normal eye motility The upper eyelid forms on abtuse angle during its elevation on abduction of the eye ball

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In one normal subject an increment of electrical activity of the Levator Palpebrae was found during maximal abduction of the eye ball (Fig 8)

Table II

Elevation of the upper eyelid on abduction and adduction in 133 normal subjects according to age

Age	No of sub jects	Number of cases showing elevation of the eyelid on						No elevation
		Abduction		Adduction		*Abduction* & adduction		
		both eyes	eye one	both eyes	one eye	both eyes	one eye	both eyes
5–10μ	4	3 (75 %)	–	–	1	–	–	–
10–20μ	10	7 (70 %)	–	3 (30 %)	–	–	–	–
20–30μ	36	23 (76 %)	–	7 (18 %)	4	2 (6 %)	–	–
30–40μ	41	15 (36 %)	8	4 (9 %)	1	10 (24 %)	–	3 ([illegible])
40–50μ	25	8 (31 %)	1	1 (4 %)	–	5 (20 %)	–	10 (40 %)
50–60μ	17	–	–	–	–	–	–	17 (100 %)
All	133	56	9	15	6	17	–	30



Fig 7

Subject with bilateral 6th nerve paresis Note exaggerated elevation of each upper lid during attempted abduction

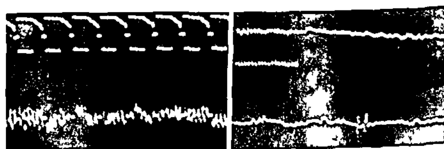


Fig 8

Electromyography of the Levator Palpebrae

a Electrical potential during primary position of the eye ball

b Electrical potential during abduction of this eye

Amplitude 300 microvolts Duration 0 1 milli/second

Discussion

Friedenwald (1896) suggested that abnormal nuclear connections were present in the cases in which elevation of the upper lid occured abduction or adduction From the present study we observed that elevation of the upper lid during horizontal movements of the eyeball is very common in normal subjects It was present in abduction on 49 % of normal subjects on adduction in 15 % and following both abduction and adduction it occured in 14 %

The change in the eyelid position described could be interpreted either on a passive movement produced by the eyeball displacing the upper lid upwards or could be an active coconcentration of the eyelid elevators and the horizontal muscles by simultaneous innervational impulses Two facts suggest the possibility of the latter mechanism as the cause of the synkinesis Among 30 subjects no lid elevation was noted although these patients as a group showed no special tendency for enophthalmus Under the passive theory some degree of enophthalmus should be present to make understandable those cases in which no upper lid elevation occurs In the only case in which electromyography was performed an increment of the electrical activity of the Levator palpebrae occured during abduction of the eye

The elevation of the eyelid on abduction in cases of paresis of the 6th nerve and Duane s syndrome would appear to be due to an exaggeration of the physiological synkinesis The synkinetic Levator palpebrae muscle could *receive* an exaggerated innervational impulse as the result of the paresis of the horizontal *muscle It would* therefore appear to be unnecessary to invoke the presence of a pathological synkinesis as does *Kestenbaum* (1961) or to explain it by abnormal *nuclear* connections as suggested by *Friedenwald* (1893)

Summary

The motility of the upper eyelid was investigated in 133 subjects with normal eye motility during horizontal movements of the eyes Elevation was found to be present in abduction in 49 % or the cases in adduction in 15 % and during both abduction and adduction it occured in 14 % An E M G in one case showed an increment of the electrical activity of the Levator palpebrae during abduction of the eye

Six cases with abducens palsy and three cases with Duane s syndrome presented exaggerated elevation of the eyelid in abduction

The presence of physiologic synkinesis between the lid elevators and the ho

rizontal muscles of the eye is suggested In cases of 6th nerve palsy and Duane's syndrome the exaggerated nerve impulses to the Levator Palpebrae muscle could be the cause for the exaggerated lid retraction on abduction

Acknowledgement

I would like to thank Professor I C Michaelson for his advice and assistance in preparing this study

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From the University of Bergen School of Medicine
Department of Ophthalmology
(Head Professor Torstein I Bertelsen M D)

THE SAGITTAL GROWTH OF THE EYE

1 Ultrasonic measurement of the depth of the anterior chamber from birth to puberty

BY

JON S LARSEN

Helmholt (1855) was the first to describe an optical method of measuring the depth of the anterior chamber *in vivo* This method was modified by *Mandelstam & Scholer* (1872) and in the same year *Donders* published a description of his measuring technique Since then a number of optical methods for this purpose has been described by *Lindstedt* (1914) *Ulbrich* (1914) *Jaeger* (1952) and others

Several photographic techniques have been recommended for the measurement of the depth of the anterior chamber by *Goldmann* (1940) *Heim* (1941) and others It is alleged that the depth of the anterior chamber can be measured by these methods to an accuracy of 0 02 mm

The possibility of using ultrasound to make biometric measurements in ophthalmology was demonstrated by the pioneer work of *Mundt & Hughes* (1956) and by *Oksala & Lehtinen* (1957) Since the beginning of the 1960 s numerous works have been published on the measurement of intraocular distances (*Yamamoto Namiki Baba & Kato* 1961 *Franken* 1961 *Purnell & Sokollu* 1962 *Gernet* 1963 1964 1965 *Gernet & Hollwich* 1968 *Jansson* 1963 *Nover & Grote* 1965 *Luyckx* 1966 *Nakajima & Kimura* 1966 *Weekers Luyckx/Bacus & Weekers* 1966 *Itin & Brawand* 1968 *Lowe* 1968 *Pallin* 1969)

It has been claimed that the ultrasonic measuring technique is not sufficiently accurate (*Baum & Greenwood* 1961 *Baum* 1967) Others have found the method both suitable and accurate *Jansson* (1963) measured the depth of the an

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terior chamber by ultrasonography (*interferometer reading*) *and by means of Stenstrom s* apparatus (*Lindstedt s* principle) and found good agreement between the two methods *with a mean difference of* – *0 034 mm for men and* 0 018 *for* women *Lowe* (1968) compared ultrasonographic and optical measurements *made with Jaeger s instrument and found a mean difference of* – *0 07*ı mm (optical minus ultrasonic) He considered it possible to measure the depth of *the anterior chamber by ultrasonography (photographic reading)* within an accuracy of ± 0 1 mm

Considerable work has been done on the problem of *determining* the depth of the anterior chamber in adults (*Lindstedt* 1913 *Raeder* 1922 *Rosengren 1930 Stenstrom 1946 Tornquist 1953 Weekers & Grieten 1961* and others) The investigations show that in adults the depth of the anterior chamber decreases with increasing age and that the depth is greater *in myopes than in* hypermetropes However there have been relatively few studies of the depth *of the anterior chamber in the postnatal period of growth and up to puberty* Our knowledge of the depth of the anterior chamber in this period is based *mainly on studies made by Calmettes Deodate Huron & Bechac* (1958) *Sorsby Benjamin & Sheridan* (1961) *Gernet* (1964) *Gernet & Hollwich* (1968) and *Luyckx (1966)* Table *1 shows the results of these studies which* were carried out with various measuring techniques

Our knowledge of the longitudinal growth of the eye after birth is incomplete The ultrasonographic technique has the advantage that it permits not only *measurement of the depth of the anterior chamber* but also of the thickness of the crystalline lens and the distance from the lens to the retina This permits *the relationship of these values to be determined* and makes it possible by measuring different age groups to obtain information on the rate of growth in *the different segments of the eye*

The purpose of this work is to examine the development of the depth of the anterior chamber from birth until the eye has reached full growth and to analy e the results in relation to the ocular refraction In subsequent papers the findings will be viewed in relation to the thickness of the lens and the depth of the corpus vitreum

In determining the depth of the anterior chamber most authors (including those mentioned in table 1) have included the thickness of the cornea This has also been done in this study

Material

The study comprises 80 full term newborns 43 boys and 37 girls aged 1–5 days examined in the maternity department Haukeland Hospital Bergen In the age

Table 1
Depth of the anterior chamber in earlier studies

Author	Age	Depth of chamber mm (mean)		No of eyes		Method
		M	F	M	F	
Gernet	days 1–5	2 9	2 [illegible]	41	26	USG
Luyckx	days 4–7	[illegible]6	[illegible]	54	50	USG
	years					
Calmettes Deodati Huron & Bechac	4–7	3 61	3.56	[illegible]	7	Jaeger s instrument
	8–11	3 67	3 60	3	16	
	1[illegible]–15	3 74	3 6[illegible]	5	16	
Sorsby Benjamin & Sheridan	3–4	3 4	3.3	53	36	Photographic phacometry
	4–5	3.5	3.3	5[illegible]	0	
	6–7	3 4	3 4	51	51	
	7–8	3 5	3.3	60	5[illegible]	
	8–9	3.5	3 4	56	58	
	9 10	3 5	3 4	47	52	
	10–11	3 6	3 5	47	59	
	11–1[illegible]	3 5	3 5	53	[illegible]9	
	12–13	3 6	3 4	61	57	
	13–14	3.5	3.5	54	56	
	14–15	3 5	3 5	40	75	
Cernet & Hollwich	0 1	3 [illegible] 3 [illegible] (M+F)		66 (M+F)		USG

group from 6 months to 13 years 851 children 468 boys and 383 girls were examined The age group 6 months – 7 years consisted of patients admitted to the ear nose and throat department of Florida Hospital Bergen for immediate operative treatment of *otitis* or tonsillitis The age group 8–13 years consisted of patients admitted to the ear nose and throat department and the children s department of Haukeland Hospital In the case of children of less than 8 with the exception of newborns the ultrasonic examination had to be made under general anaesthesia During the first year of life few operations were

performed and the Vinydan (R) anaesthesia used for examination and often for treatment of patients of this age gave too little anaesthetic effect for ultrasonic examination of the eyes Therefore only a small number of eyes was examined in this interesting stage of the growth period

Ophthalmoscopy was performed on all those examined Only eyes with clear media and no obvious eye diseases were used Both eyes were examined in all subjects In order to avoid abnormalities due to error of refraction children with hypermetropia or myopia above 5D and anisometropia above 2D, a total of 8 boys and 6 girls were excluded In cases of astigmatism the mean value of both axes was used in calculating refraction

The compostion of the material with respect to age and sex is seen in table 2 The average degree of physical development with respect to weight and height compared with values from *Sundal s* nomogram for Norwegian children (*Sundal* 1957) is shown in table 3 There is comparatively good agreement between the average value in this study and Sundal s values with the exception that the average weight of the children of 13 years was slightly lower than that given in the nomogram From an ophthalmological point of view the children should thus be comparatively representative of their general age groups

Methods

Refraction was performed in all children with the exception of the newborns In all those examined 2 drops of 1 % cyclopentolate hydrochloride (Cyclogyl) (R) were instilled into the conjunctival sac twice at intervals of about 10 min After 30–60 min a streak retinoscopy was done Children below the age of 3 were usually so restless that retinoscopy had to be performed under general anaesthetic prior to a scheduled operation

Measuring technique A Siemens Echo ophthalograph (Krautkramer system) type USIP 10 and a transducer 5 mm in diameter with a frequency of 6 MHz was used for the ultrasonic examination The apparatus was used with maximum amplification (Verstarkung 10) and impulse power (Impulsstarke 5)

The contact glass employed was of a type similar to that used by *Jansson* (1963) (constructed by *Sundmark* 1960) but with the difference that the transducer could move freely in the contact glass Newborns were examined with a contact glass with a distal diameter of 11 5 mm older children with a contact glass with a diameter of 18 mm The distal end of the contact glass was dipped in 2 % methyl cellulose before the glass was placed on the eye and then filled with sterile water The transducer was placed in the contact glass at a distance of approx 5 mm from the surface of the cornea The examiner supported the contact glass with his left hand to reduce the pressure against the eye as much as possible holding the transducer with his right hand at right angle to the surface of the cornea As soon as the echogram showed maximal amplitudes from the reflecting media (the surface of the cornea the anterior and posterior surfaces of the lens and the posterior wall of the eye) it was photographed with a Polaroid Pathfinder camera (model 120) and film type 47 by an assistant The ultrasound

Boys							Girls						
Age	Mean age (year months and days)		SD	No of subjects	No of eyes		Age	Mean age		SD	No of subjects	No of eyes
days 1–5	29 d		–	43	86		days 1–5	2 7 d		–	37	74
months 6–9	–		–	3	6		months 6–9	–		–	2	4
years	y	m	m				years	y	m	m		
1-2	1	8	3 1	18	36		1–2	1	7	3 [illegible]	11	22
2-3	2	5	3 3	59	118		2–3	2	5	3 5	52	104
3-4	3	5	2 8	55	110		3-5	3	5	3 5	45	90
4-5	4	4	3 3	50	100		4–5	4	5	3 4	33	66
5-6	5	4	3 5	32	64		5–6	5	5	3 3	23	46
6-7	6	5	5 3	32	64		6–7	6	5	3 7	32	64
7-8	7	5	3 5	35	70		7–8	7	6	3 3	25	50
8-9	8	5	3 0	50	100		8–9	8	6	3 5	16	32
9-10	9	6	4 0	40	80		9–10	9	6	3 8	24	48
10–11	10	5	2 5	28	56		10–11	10	5	3 5	22	44
11–12	11	6	3 1	26	52		11–12	11	5	3 0	36	72
12–13	12	6	3 6	28	56		12–13	12	5	3 1	38	76
13–14	13	6	3 3	12	24		13–14	13	4	3 1	24	48
Total				511	1022		Total				420	840

Table 3

Height and weight in relation to age and Sundal s nomogram values

Boys

Age (days months years)	Height cm Mean	Height cm S D	Nomo gram values (Sundal)	Weight kg Mean	Weight kg S D	Nomo gram values (Sundal)
1–5 d	50 5	–	52 0	3 5	–	3 5
6 m	70 0	–	69 0	6 5	–	8 3
9 m	77 0	–	73 0	9 5	–	9 6
Mean y m						
1 8	84 8	5 2	82 5	11 4	1 2	12 2
2 5	92 4	4 0	91 0	13 4	1 7	11 2
3 5	100 6	4 1	99 0	15 2	1 7	16 0
4 4	107 0	4 5	105 5	17 2	2 8	17 6
5 4	112 8	5 4	112 5	18 8	2 3	19 6
6 5	120 1	3 7	119 5	21 9	4 1	22 4
7 5	125 1	5 5	126 0	24 1	4 3	25 1
8 5	130 6	5 5	131 0	26 9	3 6	27 7
9 6	135 2	6 4	136 5	31 2	7 7	30 7
10 5	139 2	6 6	141 0	32 8	8 6	33 5
11 6	147 9	5 9	146 3	36 9	6 7	36 8
12 6	152 4	6 7	152 0	38 9	4 5	41 0
13 [illegible]	156 8	4 7	158 5	42 2	2 3	46 0

Girls

Age (days months years)	Height cm Mean	Height cm S D	Nomo gram values (Sundal)	Weight kg Mean	Weight kg S D	Nomo gram values (Sundal)
1–5 d	50 0	–	50 0	3 5	–	8 9
6 m	68 0	–	66 5	7 0	–	7 5
9 m	68 0	–	71 2	7 0	–	8 9
Mean y m						
1 7	82 [illegible]	6 7	81 0	10 9	1 7	11 4
2 5	90 7	5 5	89 0	12 6	4 5	13 4
3 5	98 6	4 5	97 0	14 6	1 6	15 6
4 5	105 8	4 0	104 5	16 5	1 7	17 4
5 5	112 4	5 2	112 0	19 2	2 8	19 6
6 5	116 5	6 0	118 5	20 2	2 9	22 0
7 6	123 4	4 8	125 0	21 3	2 3	24 6
8 6	127 6	4 5	130 0	25 5	2 8	27 [illegible]
9 6	135 8	4 8	135 5	28 8	3 4	30 5
10 5	148 9	9 5	146	35 5	4 6	37 2
11 5	148 9	9 [illegible]	146 5	35 5	4 6	37 2
12 5	152 3	9 1	152 0	43 4	9 1	42 0
13 4	1 48	8	1 [illegible] 0	44	7 0	46 4

beam will then coincide as closely as possible with the optic axis Fig 1 and fig 2 show the echograms from a newborn and a 4 year old boy

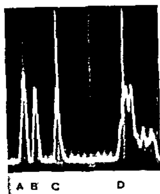


Fig 1

Normal echogram of the eye of a newborn A) Anterior corneal surface B and C) Echoes of the anterior and posterior surface of the lens D) Echo of the posterior pole of the eye

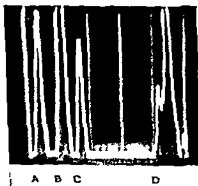


Fig 2

Photo of a typical echogram from a 4 year old boy (A Corneal echo B and C Lens echoes D Posterior pole echo)

Newborns were examined lying flat in their beds the head being held steady by an assistant The eyes were measured after application of a few drops of oxibuprocaine 0 ** or tetracaine This age group was not measured under cycloplegia.

Table 3

Height and weight in relation to age and Sundal s nomogram values

Boys							Girls						
Age (days months years)	Height cm		Nomo gram values (Sundal)	Weight kg		Nomo gram values (Sundal)	Age (days months years)	Height cm		Nomo gram values (Sundal)	Weight kg		Nomo gram values (Sundal)
	Mean	S D		Mean	S D			Mean	S D		Mean	S D	
1–5 d	50 5	–	52 0	3 5	–	3 5	1–5 d	50 0	–	50 0	3 5	–	8 9
6 m	70 0	–	69 0	6 5	–	8 3	6 m	68 0	–	66 5	7 0	–	7 5
9 m	77 0	–	73 0	9 5	–	9 6	9 m	68 0	–	71 2	7 0	–	8 9
Mean y m							Mean y m						
1 8	84 8	5 2	82 5	11 4	1 2	12 2	1 7	82 [illegible]	6 7	81 0	10 9	1 7	11 4
2 5	92 4	4 0	91 0	13 4	1 7	11 2	2 5	90 7	5 5	89 0	12 6	4 5	13 4
3 5	100 6	4 1	99 0	15 2	1 7	16 0	3 5	98 6	4 5	97 0	14 6	1 6	15 6
4 4	107 0	4 5	105 5	17 2	2 8	17 6	4 5	105 8	4 0	104 5	16 5	1 7	17 4
5 4	112 8	5 4	112 5	18 8	2 3	19 6	5 5	112 4	5 2	112 0	19 2	2 8	19 6
6 5	120 1	3 7	119 5	21 9	4 1	22 4	6 5	116 5	6 0	118 5	20 2	2 9	22 0
7 5	125 1	5 5	126 0	24 1	4 3	25 1	7 6	123 4	4 8	125 0	21 3	2 3	24 6
8 5	130 6	5 5	131 0	26 9	3 6	27 7	8 6	127 6	4 5	130 0	25 5	2 8	27 5
9 6	135 2	6 4	136 5	31 2	7 7	30 7	9 6	135 8	4 8	135 5	28 8	3 4	30 5
10 5	139 2	6 6	141 0	32 8	8 6	33 5	10 5	148 9	9 5	146 5	35 5	4 6	37 2
11 6	147 9	5 9	146 3	36 9	6 7	36 8	11 5	148 9	9 5	146 5	35 5	4 6	37 2
12 6	152 4	6 7	152 0	38 9	4 5	41 0	12 5	152 3	9 1	152 0	43 4	8 1	42 0
13 6	156 8	4 7	158 5	42 2	2 3	46 0	13 4	154 8	5 8	156 0	44 5	7 0	46 4

The velocity of the ultrasonic beam = k m/sec. The length of the echo of the water column = Lwe = k Tw =

$$k = \frac{2Lw}{Vw} \text{ metres (II)}$$

The measurement of an unknown distance in the eye 2Lo gives an echo length = Loe The time elapsing from the ultrasonic beam is emitted until the echo returns =

$$To = \frac{2Lo}{Vo} \text{ (III)}$$

where Vo = the velocity in the eye

$$\text{The length of the echo} = Loe = k\ To = k\ \frac{2Lo}{Vo} \text{ (IV)}$$

From (IV) the distance sought will be

$$Lo = \frac{Loe\ Vo}{2k} \text{ (V)}$$

$$\text{According to (II) } k = \frac{Lwe\ VW}{2Lw} \text{ which inserted in (V) gives}$$

$$Lo = \frac{Loe\ Vo}{\frac{2\ Lwe\ Vw}{2Lw}} = \frac{Lw\ Vo}{Lwe\ Vw}\ Loe.$$

The echo reading for the intraocular distances must thus be multiplied by the factor $\frac{Lw\ Vo}{Lwv\ Vw}$

The respective ultrasound velocities in the anterior chamber the lens and the corpus vitreum are inserted in the place of Vo

The velocity of ultrasound in aqueous humour at 37 C is approx 1532 m/sec (*Jansson* 1963) and in sterile water (Vw) at 20 C 1482 m/sec As Lw was found to be approximately equal to Lwe the depth of the anterior chamber Lcam = $LcamE \cdot \frac{1532}{1482}$ = LcamE 1 03 where LcamE is the length of the echo of the anterior chamber LcmaE was measured from the photograph to an accuracy of 1/10 mm The depth of the anterior chamber was then determined by multiplying this value by 1 03

Error of the method A systematic error occurs in the measurements because the thickness of the central cornea is included when the depth of the anterior chamber is measured The velocity of ultrasound in the cornea at 37 C is stated by *Rivara & Sanna* (19?) to be 1586 m/sec and by *Tschewnenko* (1965) 1639 m/sec Putting the central corneal thickness at 0.57 mm (*von Bahr* 1948) and the approximate value of the velocity of ultrasound at 1600 m/sec gives an addition to the desired measurement of 0 02 mm (Putting the velocity of ultrasound at 1639 m/sec gives an addition of 0 03 mm)

This measurement error has not been subtracted from the values given in this study

Other measurement errors may possibly have arisen by

1 The ultrasound beam not following the optical axis

Jansson (1963) and *Pallin* (1969) have calculated the deviation for intraocular distances caused by a beam path at an angle to the optical axis According to Jansson's calculations in which a method similar to that of this study was used a distance measured in the anterior chamber with an angle deviation of 5° will be approximately 0 01 mm longer than along the optical axis The calculations were based on Gullstrand's schematic eye in which the distance from the corneal vertex to the front of the lens is 3 60 mm

The age group 6 months to 7 years was examined under a general anaesthetic while lying on the operating table prior to an operation Measurements were made under cycloplegia induced by 1 % cyclopentolate hydrochloride In the age group 8 to 13 years surface analgesia (oxibuprocaine or tetracaine) was adequate for measurements and the eyes were measured under cycloplegia Children in this group were examined lying on an examination couch A small lighted bulb on the ceiling directly above the eye to be measured served as fixation point

Calibration of the apparatus Before use the oscilloscope adjustment was checked on the calibration bar of the apparatus The calibration bar corresponded to 25 mm fluid with an ultrasonic velocity of 1482 m/sec Prior to computation of the intraocular distances the linearity of the oscilloscope scale was investigated by connecting the transducer to a micrometer caliber and lowering it via a perpendicular guide cylinder into sterile water with a temperature of 20°C The echo from the bottom of the plexiglass cylinder was registered on the oscilloscope screen each time the length of the water column was increased by 0 5 mm The whole scale was investigated in this way The echo signals were in accordance with the scale calibration up to 18 mm water column The section of the scale above 18 mm however showed deviation from the real length of the column of water The reduction on the oscilloscope scale in relation to the length of the water column is shown in fig 3 There was full linearity in the section of the scale used for measurements of the anterior chamber depth

Computation of intraocular distances

Computations of the intraocular distances were based on the following

The length of the water column used for calibration = Lw The ultrasound must move one length = 2 Lw (back and forth) The time elapsing from the time the ultrasound is emitted until the echo returns = $Tw = \frac{2Lw}{Vw}$ (I) where Vw is the velocity in water

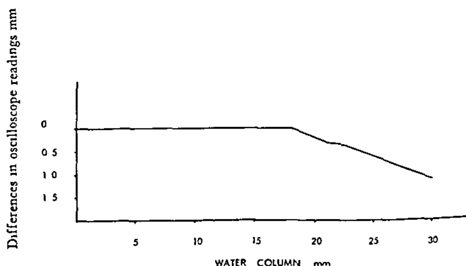


Fig 3
Calibration of oscilloscope scale (distilled water at 20°C)

Table 4

Age and refraction in the male material

Age (years)	Refraction D													No of eyes
	Myopia					±0	Hypermetropia					Mean	SD	
	5.0<4.0	4.0<3.0	3.0<2.0	2.0<1.0	1.0<0		0<1.0	1.0<2.0	2.0<3.0	3.0<4.0	4.0<5.0			
1–2			2			4	4	6	14	6		+1.51	1.26	96
2–3			2	10		10	20	42	18	14	2	+1.22	1.29	118
3–4				6	10	18	20	38	14	2	2	+0.86	1.10	110
4–5				10	4	24	30	4	6	2		+0.51	0.79	100
5–6				4	4	16	12	18	8	2		+0.67	1.00	64
6–7				2	2	10	16	28	4	2		+0.62	1.32	64
7–8		2		4	2	20	14	0	4	4		+0.61	1.22	70
8–9				4	4	20	28	40	4			+0.60	1.15	100
9–10				8		20	28	20	4			+0.48	0.78	80
10–11				4	8	12	8	16	4		4	+0.69	1.28	56
11–12					4	20	20		4		4	+0.65	1.13	52
12–13				4	12	20	0					± 0	0.63	56
13–14					8	4	8	4				+0.03	0.60	24
Scattering %		0.2	0.4	6.0	6.2	21.3	24.5	27.5	9.0	3.4	1.3			

2 Pressure from the contact glass flattening the anterior occular segment

To investigate this possibility the present author made measurements on two patients both *with swimmers goggles (which were filled with water in which the transducer was immersed)* and with the contact glass described Five measurements were made by each method on a 12 year old boy and a 13 year old girl No significant difference was found between the results Thus it does not seem that the contact glass used as in the study deformed the anterior ocular segment

In order to determine the accuracy of the method used in the study 10 different measurements were made of the right eye of the same individual The mean value of the measurements was 3 9037 mm the SD was 0 033 mm and 3SD was 0 099 mm This result is in consistence with the values obtained by *Jansson* (1963) In the case of the newborns the method gave a lesser degree of accuracy due to unfavourable examination conditions including warding off reaction and blepharospasm which increased when measurements were repeated On 3 comparatively placid children 5 measurements were made of the right eye On comparison with the first measurements the deviation in the measured value did not exceed ± 0 1 mm

Results

The distribution of ocular refraction in 465 boys and 381 girls in the age group 1–13 years is shown in tables 4 and 5 *respectively* The few observations from the first year of life all showed a hypermetropy of 1 to 4 diopters With increasing age the hypermetropy decreases From the 2nd to the 12th year of life the mean value decreases approx 1 5 diopters in boys and approx 1 6 diopters in girls

Depth of the anterior chamber Tables 6 and 7 show the depth of the anterior chamber in different age groups in boys and girls respectively The percentual distribution is shown in figs 4 and 5 During the first one and a half years of life the depth of the anterior chamber increases approx 1 0 mm in boys and approx 0 9 mm in girls In the age group 1–13 years there is an increase in the depth of the anterior chamber of approx 0 35 mm in both sexes The depth of the anterior chamber has then reached values equivalent to those of adults in the age group 20–40 years in which the mean value was 3 71 mm in 10 emmetropic men and 3 62 mm in 10 emmetropic women

These findings accord well with earlier studies on adults in corresponding age groups *Lindstedt* (1913) found a mean value for both sexes of 3 68 mm *Stenstrom* (1948) found a mean value of 3 70 mm for men and 3 65 for women

The increase in the depth of the anterior chamber describes an asymptotic curve as shown in fig 6 Except for the newborns the mean value of the anterior chamber depth is higher for boys in all age groups Table 8 shows the difference between the mean values for boys and girls in the various year classes In the age group 1–13 years the difference between the mean values is significant 0 08 ± 0 0173 mm As table 8 shows the difference is not significant for the

Table 6

Depth of the anterior chamber in the present male series

Depth of chamber mm	Age															
	Days	Months		Years												
	1 5	6	9	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12	12-13	13-14
2.15-2.24	17															
2.25-2.34	1															
2.35-2.44	34															
2.45-2.54	6															
2.55-2.64	6															
2.65-2.74	2	2	1													
2.75-2.84			1													
2.85-2.94					2											
2.95-3.04					2	2		2	4							
3.05-3.14			1	2	4								4			
3.15-3.24			1	15	21	12	10	8	2	4	2				4	
3.25-3.34				3	30	0	14	6	12	8	4	4	8	4	2	
3.35-3.44				6	21	16	18	12	8	11	18	2		8	6	4
3.45-3.54				6	17	22	25	10	10	11	18	18	4	8	8	2
3.55-3.64					5	9	8	8	7	6	14	24	6	6	8	6
3.65-3.74					8	10	9	4	9	10	24	20	8	10	8	
3.75-3.84				3	3	9	4	4	2	8	6	8	14	4		4
3.85-3.94				1	2	3	8	6	2	4	6		6	12	8	6
3.95-4.04					3	5		2	4	4	2	4	6		6	2
4.05-4.14						2		2	2	1	4					
4.15-4.24							4		2	3	2				4	
4.25-4.34																
4.35-4.44																
4.45-4.54																
4.55-4.64															2	
Number of eyes	66	2	4	36	118	110	100	64	64	70	100	80	56	52	56	24
Mean	2.37	2.68	2.94	3.35	3.38	3.50	3.5[illegible]	3.52	3.54	3.61	3.63	3.63	3.66	3.64	3.71	3.70
SD	0.12	–	–	0.22	0.22	0.30	0.25	0.28	0.27	0.20	0.23	0.15	0.12	0.22	0.32	0.22
SE	0.013	–	–	0.036	0.021	0.029	0.025	0.03	0.034	0.024	0.023	0.017	0.037	0.031	0.043	0.045

Table 5

Age and refraction in the female material

Age (years)	Refraction D											Mean	S D	*No of eyes*
	Myopia						Hypermetropia							
	5 0<4 0	4 0<3 0	3 0<2 0	2 0<1 0	1 0<0	±0	0<1 0	1 0<2 0	2 0<3 0		4 0<5 0			
1– 2				4				6	6	6		+ 1 59	1 81	22
2– 3				4	6	22	30	28	8	6		+ 0 69	0 95	104
3– 4					2	20	26	22	20			+ 0 90	0 85	90
4– 5						8	12	20	18	6	2	+ 1 55	1 06	66
5– 6				2	2	6	8	16	12			+ 0 98	0 96	46
6– 7		2	2	2	2	2	16	16	14	10		+ 0 52	1 28	64
7– 8	2				4	8	16	16	4			+ 0 56	1 32	50
8– 9				4		8	4	16				+ 0 44	0 89	32
9–10				4		12	24	8				+ 0 33	0 78	48
10–11			4	4	24	4	4	4				+ 0 05	1 13	44
11–12				8		4	32	16	12			+ 0 04	0 86	72
12–13	8		8	4		28		16	4	4	4	+ 0 03	2 11	76
13–14				4	8		12	16	8			0	1 04	48
Scattering %		1 3	0 3	3 4	4 7	25 7	22 6	24 4	11 3		0 8			

Table 6

Depth of the anterior chamber in the present male series

Depth of chamber mm	Age															
	Days	Months		Years												
	1–5	6	9	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–11	11–12	12–13	13–14
2.15–2.24	17															
2.25–2.34	21															
2.35–2.44	34															
2.45–2.54	6															
2.55–2.64	6															
2.65–2.74	2	2	1													
2.75–2.84			1													
2.85–2.94					2											
2.95–3.04					2	2		2	4							
3.05–3.14			1	2	4								4			
3.15–3.24			1	15	21	12	10	8	2	4	2				4	
3.25–3.34				3	30	20	14	6	12	8	4	4	8	4	2	
3.35–3.44				6	21	16	18	12	8	11	18	2		8	6	4
3.45–3.54				6	17	22	25	10	10	11	18	18	4	8	8	2
3.55–3.64					5	9	8	8	7	6	14	24	6	6	8	6
3.65–3.74					8	10	9	4	9	10	24	20	8	10	8	
3.75–3.84				3	3	9	4	4	2	8	6	8	14	4		4
3.85–3.94				1	2	3	8	6	2	4	6		6	12	8	6
3.95–4.04					3	5		2	4	4	2	4	6		6	2
4.05–4.14						2		2	2	1	4					
4.15–4.24							4		2	3	2				4	
4.25–4.34																
4.35–4.44																
4.45–4.54																
4.55–4.64															2	
Number of eyes	86	2	4	36	118	110	100	64	64	70	100	80	56	52	56	24
Mean	2.37	2.68	2.94	3.35	3.38	3.50	3.52	3.52	3.54	3.61	3.63	3.63	3.66	3.64	3.71	3.70
SD	0.12	–	–	0.22	0.22	0.30	0.25	0.28	0.27	0.20	0.23	0.15	0.12	0.22	0.32	0.22
SE	0.013	–	–	0.036	0.021	0.029	0.025	0.03	0.034	0.024	0.023	0.017	0.037	0.031	0.043	0.045

Table 7
Depth of the anterior chamber in the present female series

Depth of chamber mm	Age															
	Days	Months		Years												
	1–5	6	9	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–11	11–12	12–13	13–14
2.05–2.14	3															
2.15–2.24	7															
2.25–2.34	13															
2.35–2.44	32															
2.45–2.54	9															
2.55–2.64	10															
2.65–2.74		2														
2.75–2.84				1												
2.85–2.94				1												
2.95–3.04							2				2					
3.05–3.14				2	2			2		2			2		4	
3.15–3.24				12	43	28	16	11	8	1	6		6	8	8	4
3.25–3.34				2	19	18	13	10	16	6		8		4	8	
3.35–3.44				5	14	20	11	5	14	3	6	8	6	4		16
3.45–3.54				1	8	10	14	8	14	10	2	2	6	6	12	4
3.55–3.64					4	12	6	2	2	6	4	20	4	16	12	2
3.65–3.74					7	2	4	6	6	10		2	4	18	14	6
3.75–3.84					3			2		6		4	4		14	2
3.85–3.94					4					5	4	4	7	8		8
3.95–4.04									2	1	4		5	8		6
4.05–4.14									2		4					
4.15–4.24															4	
Number of eyes	74	2	2	22	104	90	66	46	64	50	32	48	44	72	76	48
Mean	2.39	2.68	2.83	3.24	3.3[illegible]	3.3	3.37	3.39	3.44	3.59	3.[illegible]0	3.[illegible]6	3.[illegible]9	3.63	3.57	3.62
SD	0.12	–	–	0.10	0.22	0.24	0.17	0.20	0.19	0.29	0.19	0.19	0.34	0.2	0.29	0.34
SE	0.014	–	–	0.021	0.022	0.02[illegible]	0.021	0.029	0.021	0.041	0.034	0.028	0.0[illegible]2	0.02[illegible]	0.033	0.049

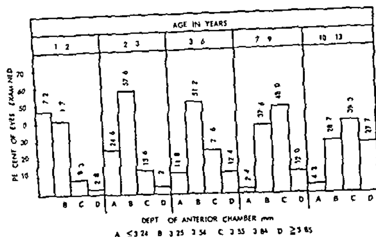


Fig 4
Percentage distribution of the anterior chamber depth in the male material

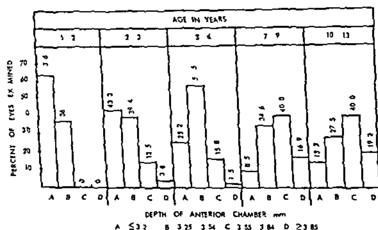


Fig 5
Percentage distribution of the anterior chamber depth in the female material

age group 7—9 years Nevertheless it seems probable that there is a real sex determined difference in the depth of the anterior chamber during the whole period of growth This factor is reflected in the different refraction forms Among the youngest children it was the age group 1–3 years that showed the

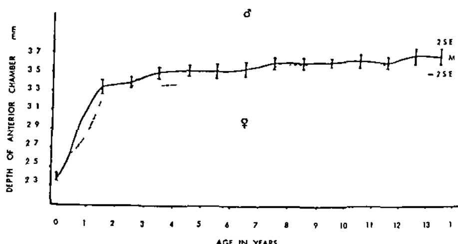


Fig 6
Average growth curve for the depth of anterior chamber

Table 8
The mean values of the anterior chamber depth in age groups and the statistical significance of the difference between the sexes (Student T – test)

		Age in years			
		1 – 2	2 – 6	7 – 9	10 – 13
Depth of chamber	Boys	3 35	3 48	3 62	3 68
mm	Girls	3 24	3 37	3 58	3 60
Differences		0 11	0 11	0 04	0 08
P values		0 01<P<0 05	P<0 001	P>0 05	P<0 01

greatest relative dispersion in refraction (tab 4 and 5) In this age group the mean values for the different forms of refraction were as follows

	Myopia	Emmetropia	Hypermetropia
	(– 1D – – 2 5D)	(– 0 75D – + 0 75D)	(+ 1D – + 4 5D)
Boys	3 64 mm	3 50 mm	3 36 mm
Girls	3 47 mm	3 35 mm	3 31 mm

For myopes (38 eyes) the difference between the two sexes was 0 17 mm for emmetropes (192 eyes) 0 15 mm and for hypermetropes (260 eyes) 0 05 mm Tab 9 shows the mean value of the anterior chamber depth for the different forms of refraction in the year classes below 4 years The difference in the anterior

Table 9

The mean depth of anterior chamber (mm) the mean difference in chamber depth and the statistical significance between hypermetropia emmetropia and myopia for boys and girls and between sexes (Student T – test)

		Age in years 1–2	2–3	3–4	Mean Differences	Total P values	No of eyes
Boys	M	3 87	3 71	3 57	3 64 > 0 14	0 05 < P < 0 1	20
	E	3 39	3 40	3 56	3 50 > 0 14	< 0 01	86
	H	3 25	3 34	3 43	3 36		158
Girls	M	3 34	3 66	–	3 47 > 0 19	0 01 < 1 < 0 05	8
	E	–	3 34	3 36	3 55 > 0 04		106
	H	[illegible]	3 30	3 33	3 31		102
Differences	M	0 53	– 0 06	–	0 17		
	E	–	0 06	0 20	0 15	< 0 01	
	H	0 04	0 04	0 10	0 05	< 0 01	

M = Myopia Γ = Emmetropia H = Hypermetropia

chamber depth between the two sexes was significant for emmetropes and hypermetropes (0 001<P<0 01) The number of myopes was so small that a significance computation would not have given realistic values

The difference in the mean value between emmetropes and hypermetropes was significant for both boys (0 001<P<0 01) and girls (0 01<P<0 05) (tab 9) On the other hand the difference in the anterior chamber depth between myopes and emmetropes (for boys in whom the number of myopes was greatest) was not significant (0 05<P<0 1) This is a finding which might have been expected as the material consisted only of lighter degress of myopia

For older children the relation between the depth of the anterior chamber (y) and refraction (x) was computed for 12 year old girls (76 eyes) where refraction was between +5D and -5D A significant negative correlation was found between the anterior chamber depth and refraction

Regression line
$$y = 3\ 5750 - 0\ 1177\ x$$
$$r = -0\ 8847$$
$$\varepsilon r = 0\ 0548$$
$$P < 0\ 001$$

This relationship is shown graphically in fig 7

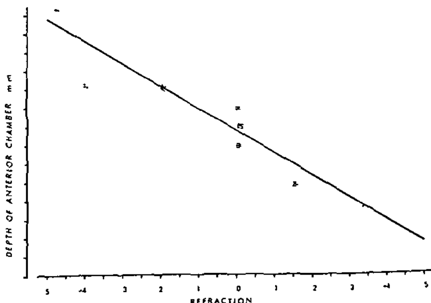


Fig 7

Correlation between depth of anterior chamber and refraction girls aged 12 years (76 eyes) Regression line y = 3 5750 - 0 117x X

In the other year classes the dispersion was too small to give realistic values on statistical computation (tab 4 and 5)

Discussion

The results of this study showed a decrease in ocular refraction of 1 5 – 2D from the age of one and a half to 12 years in both girls and boys A similar gradual reduction in refraction was found in public health surveys in the U S A and Great Britain with reductions from + 2 5D at the age of 2 to + 0 75D at the age of 12 (*Knightoon* 1939) *Sorsby Benjamin & Sheridan* (1961) found a gradual reduction from approx + 2 5D at the age of 3 to approx + 1D at the age of 12 However *Brown* (1938) and *Slapter* (1950) found an increase in hypermetropy of approx 1 6D from early infancy to the age of 7 and a reduction of approx °D in the following 8 years

Depth of anterior chamber If the values for the depth of the anterior chamber in newborns in this study are compared with the values given by *Gernet* (1964) and *Luyckx* (1966) it will be found that Gernet s results give an anterior chamber that is approx 0 5 mm deeper and Luyckx approx 0 1 to 0 2 mm deeper The fact that these authors made their examinations under cycloplegia must however be taken into consideration Gernet made use of a technique in which the probe was placed directly on the cornea a method which is more apt to give deformation of the anterior ocular segment and in which there in no corneal echo There is therefore reason to believe that the results of Gernet s measurements may be less precise than those of the present study It has long been known that the depth of the anterior chamber in adults increases on paralysis of accommodation after the instillation of homatropine or atropine and decreases on accomodation (*Heim* 1941 *Karpe* 1938) In 8 years olds *Calmettes Deodati Huron & Bechac* (1958) found that the anterior chamber depth increased under atropine cycloplegia by 0 38 mm and 0 20 mm respectively compared with measurements made at maximum accommodation (2 *cases*) *It is* however not known whether the anterior chamber depth in newborns is altered by *cycoplegia* In order to study this more closely measurements were carried out on 3 newborns The right eyes were first measured 5 times without cycloplegia (I) and then 5 times under cyclopentolate hydrochloride/metaoxedrin cycloplegia (*II*)

The following mean values were obtained

	I	II
	mm	mm
1	2.35	2.37
2	2 41	2 37
3	2 64	2 66

There is no significant difference between the two groups The depth of the anterior chamber in newborns does not seem to be affected by cycloplegia The values must however be interpreted with caution as the unrest appearing in this age group on repeated measurements may influence the results

No other data appear to be available on the depth of the anterior chamber in the first year of life than those given by *Gernet & Hollwich* (1968) The mean value of the anterior chamber depth for the age group 0–2 years (15 eyes) is given as 2 96 mm This value accords well with the values found in this study in a corresponding age group

The values found in this study for older children are in good accord with those found by *Calmettes Deodati Huron & Bechac* (1958) in emmetropic eyes *Sorsby Benjamin & Sheridan* (1961) found values of approx 0 1 mm in the age group 3–13 years although the fact that *Sorsby et al* were working with a more hypermetropic material must be taken into consideration

According to the results of this study the increase in the anterior chamber depth from birth to puberty can be divided into three growth phases (tab 6 and 7 and fig 4 5 and 6) A rapid postnatal growth phase lasting until the age of one and a half years during which the anterior chamber depth increases by approx 0 9–1 0 mm in both sexes followed by a slower infantile growth phase from 1–7 years during which the anterior chamber depth increases by approx 0 3–0 4 mm and finally a slow juvenile growth phase from 8–13 years with an increase of barely 0 1 mm In this study no difference was found between the values for the anterior chamber depth at the age of 13 and the values for em metropic adults in the age group 20–40 years It would therefore appear that the depth of the anterior chamber no longer increases or increases only very slightly after the age of approx 13 *Sorsby et al* (1961) working on a very large material also found that the growth of the anterior chamber was complete at about the age of 13 A similar early termination of the increase in the depth of the anterior chamber was given by *Weekers & Grieten* (1961) and by *Wee kers Luyckx-Bacus & Weekers* (1966) *Calmettes Deodati Huron & Bechac* (1958) on the other hand found the average depth of the anterior chamber to be 0 08 mm greater in the age group 16–20 years than in the age group 12–15 years

Gernet & Hollwich (1968) carried out ultrasonar measurements of buphthal mic eyes in a comparative study including 66 emmetropic healthy eyes with a view to establishing the growth rate of the ocular axis The study which cov ered the age group 0–12 years appears to be the only study in living eyes which covers the whole period of growth from birth to puberty With regard to the depth of the anterior chamber however only the mean value for all year classes (0–12 years) is stated being given as 3 20 ± 0 329 mm The sex and age distribution of Gernet & Hollwich s material is however not known and the mean value for the anterior chamber depth cannot without reserve be com

pared with the values found in this study For the growth period as a whole Gernet s value is however lower than the mean values found in this material

In adults the mean value of the anterior chamber depth appears to be greater in men than in women *Rosengren s* material (1930) was investigated with regard to this by *Tornquist* (1953) The difference found 0 08±0 023 mm was statistically significant *Stenstrom* (1946) and *Tornquist* (1953) found a difference of 0 05±0 020 mm and 0 09±0 035 mm respectively It seems probable that there is a real difference in the depth of the anterior chamber between the two sexes although the difference found was not statistically significant

Calmettes et al (1958) measuring emmetropes found a difference between the two sexes in the age group 4–7 years (9 eyes) of 0 05 mm in the age group 8–11 years (19 eyes) of 0 07 mm and in the age group 12–15 years (21 eyes) of 0 09 mm

In this investigation series there was no difference at birth between the anterior chamber depth of the two sexes However growth is more rapid in boys throughout the first years and in the age group 1–2 years there was a difference of the order of 0 1 mm which remained unchanged to the age group 7–9 years when the difference was reduced to less than the difference found in adults (tab 8) This finding reflects the general growth curve for height and weight (cf tab 3) Although the difference in anterior chamber depth is not significant for the age group 7–9 years it nevertheless appears probable that there is a real difference in the depth of the anterior chamber between the two sexes in this age group also

The relation between the depth of the anterior chamber and refraction in newborns and in the first year of life is not known From the age of one year however there is a negative correlation the anterior chamber being deeper in myopes than in hypermetropes

Summary

Ultrasonographic measurements of the depth of the anterior chamber were carried out in 80 full term newborns (43 boys and 37 girls) and in 465 boys and 381 girls aged 6 months to 13 years Both eyes were measured in all subjects From birth to the age of 13 the mean value of the anterior chamber depth increased from 2 37 to 3 70 mm for boys and from 2 39 to 3 62 mm for girls having then reached the same value as in young adults (20–40 years) It therefore appears that the increase in the depth of the anterior chamber terminates at the age of 13 or is minimal after this age The increase in the depth of the anterior chamber takes place in three growth phases A rapid postnatal phase from birth to the age of one and a half years with an increase of approx 0 9–1 0 mm a

slower infantile phase from 1 to 7 years with an increase of 0 3–0 4 mm and a slow juvenile phase from 8 to 13 years with an increase of barely 0 1 mm During the whole of the growth period there appears to be a real sex determined *difference in the depth of the* anterior chamber of about 0 1 mm the deepest anterior chamber being found in boys A negative correlation between the depth of the anterior chamber and refraction develops at an early stage of the growth period and has in this study been found to be established from the second year of life

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From the Eye Clinic (Head Professor G. von Bahr) Akademiska sjukhuset Uppsala and the Department of Patholo y Karolinska sjukhuset Stockholm

ENDOGENOUS FUNGUS ENDOPHTHALMITIS

BY

PER ERIK WALINDER & ERIK KOCK

Intraocular fungus infections are often difficult to diagnose and despite new fungistatic drugs they often present great therapeutic problems This communication reports 4 cases with metastatic spread of fungus infection to the eye one case with Aspergillus fumigatus endophthalmitis and 3 cases with Candida albicans endophthalmitis

Case 1

Clinical history A 38 year old man with a severe insufficiency and stenosis of the aortic valve secondary to a rheumatic fever in childhood was operated with excision of the aortic ostium and replacement with a Cutter prosthesis Postoperative fever was treated with large doses of antibiotics (penicillin, ampicillin, cloxacillin and erythromycin) and terminally with amphotericin B intravenously In spite of the therapy the patient died with signs of sepsis 2 months after the operation.

Eye signs The eyes were examined before operation and were normal Six weeks after operation the patient complained of diminishing vision in the right eye (O D) The vision was slightly reduced and there were preretinal and retinal haemorrhages in the macular region In the left eye (O S) small haemorrhages lay near the papilla

Four days later vision in the O D was reduced to l ght perception there was fibrin us exudate in the anterior chamber and the vitreous was clouded The O S was unchanged

During the following week the vitreous body of the O D became less clouded and in the central part a yellow white mass with rather distinct margins was seen In the temporal part a pear shaped body protruded from the main lesions These findings led t the su picion of a fungal infection In spite of treatment with amphotericin B intravenously and nystat n orally there was no improvement The patient died 1 week later

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Laboratory investigations Repeated blood cultures for bacteria and fungi were negative Aspergillus fumigatus was isolated from the right eye at autopsy but not from other organs

Autopsy findings Surgical excision of the aortic valve (Cutter prosthesis) endocarditis pulmonary oedema and inflammatory changes in the spleen Necrosis with mycelia was observed microscopically at the site of the aortic valve resection.

The eyes

Macroscopical examination

The O D was of normal size Grey exudate filled the vitreous body and haemorrhages were scattered over the retina

The O S was of normal size In the equatorial 2 o clock there was a preretinal haemorrhage with exudate in the vitreous body Four small haemorrhages were noted at other sites

Microscopical examination

The O D The anterior chamber contained some neutrophilic granulocytes The iris ciliary body and choroid contained only small focal infiltrations of lymphocytes and plasma cells

The retina In the whole posterior part there was oedema with neutrophilic granulocytes usually clustered around the vessels Just in front of the retinal changes posterior to the internal membrane there was a large preretinal haemorrhage containing numerous neutrophilic granulocytes (Fig 1)

In the corresponding parts of the *vitreous body* there were granulomas of different sizes composed of granulocytes and macrophages (Fig 2) With the Gomori methanamine silver nitrate stain for fungi the central parts of the granulomas were found to contain straight hyphae with branches characteristic for Aspergillus fumigatus (Fig 3) The rest of the ciliary body was diffusely infiltrated with granulocytes

The O S contained slight changes of the same type as seen in the O D

Case 2

Clinical history A 48 year old woman was operated for a ventricular septal defect. Postoperative fever was treated with large doses of antibiotics (penicillin cloxacillin chloramphenicol and ampicillin) Two and three weeks after the operation Candida albicans was cultured from blood Antibacterial therapy was then withdrawn Amphotericin was given for 7 weeks (total dose 1212 mg) then discontinued because of a transitory rise of the serum creatinine Two weeks later potassium iodide was tried as antimycotic therapy (3 g/day for 2 weeks)

Postoperative X ray revealed a rounded area of homogenous density in the left lung probably a Candida abscess The lesion gradually diminished and surgical removal was not indicated The patient s general health and heart condition was good 4 years after operation

Eye signs The eyes were examined before operation and were normal Five weeks after operation the patient noted blurring of the vision Eye examination showed a small white exudate with sharp margins localized between the optic disc and the macula of each eye



Fig 1
Case 1 O D The retina infiltrated with granulocytes and a haemorrhage under the internal limiting membrane In the vitreous bodydiffusely scattered granulomes
Htx – eosin X 30

A week later there was a severe reaction in both eyes aqueous flare cloudiness of vitreous body oedema of the papilla and macula, engorgement of the veins and the exudates in the eye grounds had enlarged Amphotericin B and prednison (?00 mg/day) were given generally and atrop n and prednisolon topically The reaction in the media then decreased but the exudates in the eye grounds specially in the O S enlarged and protruded into the vitreous General prednison was withdrawn after 2 weeks During the following weeks the exudates in both eye grounds increased

The O S showed a peculiar budd ng of the exudate The new bud at first had d stinct margins but it then became blurred and after 4–5 days another bud rather suddenly (within 10–1? hours) appeared This was repeated several times with a new bud often at the top of the last one (Fig 4 a–e)

11 weeks after operation, when amphotericin was withdrawn the exudate in the left

Laboratory investigations Repeated blood cultures for bacteria and fungi were negative Aspergillus fumigatus was isolated from the right eye at autopsy but not from other organs

Autopsy findings Surgical excision of the aortic valve (Cutter prosthesis) endocarditis pulmonary oedema and inflammatory changes in the spleen Necrosis with mycelia was observed microscopically at the site of the aortic valve resection

The eyes

Macroscopical examination

The O D was of normal size Grey exudate filled the vitreous body and haemorrhages were scattered over the retina

The O S was of normal size In the equatorial 2 o clock there was a preretinal haemorrhage with exudate in the vitreous body Four small haemorrhages were noted at other sites

Microscopical examination

The O D The anterior chamber contained some neutrophilic granulocytes The iris ciliary body and choroid contained only small focal infiltrations of lymphocytes and plasma cells

The retina In the whole posterior part there was oedema with neutrophilic granulocytes usually clustered around the vessels Just in front of the retinal changes posterior to the internal membrane there was a large preretinal haemorrhage containing numerous neutrophilic granulocytes (Fig 1)

In the corresponding parts of the *vitreous body* there were granulomas of different sizes composed of granulocytes and macrophages (Fig 2) With the Gomori methanamine silver nitrate stain for fungi the central parts of the granulomas were found to contain straight hyphae with branches characteristic for Aspergillus fumigatus (Fig 3) The rest of the ciliary body was diffusely infiltrated with granulocytes

The O S contained slight changes of the same type as seen in the O D

Case 2

Clinical history A 48 year old woman was operated for a ventricular septal defect Postoperative fever was treated with large doses of antibiotics (penicillin cloxacillin chloramphenicol and ampicillin) Two and three weeks after the operation Candida albicans was cultured from blood Antibacterial therapy was then withdrawn Amphotericin was given for 7 weeks (total dose 1212 mg) then discontinued because of a transitory rise of the serum creatinine Two weeks later potassium iodide was tried as antimycotic therapy (3 g/day for 2 weeks)

Postoperative X ray revealed a rounded area of homogenous density in the left lung probably a Candida abscess The lesion gradually diminished and surgical removal was not indicated The patient s general health and heart condition was good 4 years after operation

Eye signs The eyes were examined before operation and were normal Five weeks after operation the patient noted blurring of the vision Eye examination showed a small white exudate with sharp margins localized between the optic disc and the macula of each eye



Fig 1

Case 1 O D The retina infiltrated with granulocytes and a haemorrhage under the internal limiting membrane In the vitreous bodydiffusely scattered granulomes
Htx – eosin × 30

A week later there was a severe reaction in both eyes aqueous flare cloudiness of vitreous body oedema of the papilla and macula, engorgement of the veins and the exudates in the eye grounds had enlarged Amphotericin B and prednison (?00 mg/day) were given generally and atropin and prednisolon topically The reaction in the media then decreased but the exudates in the eye grounds specially in the O S enlarged and protruded into the vitreous General prednison was withdrawn after 2 weeks During the following weeks the exudates in both eye grounds increased

The O S showed a peculiar budd ng of the exudate The new bud at first had d stinct marg ns but it then became blurred and after 4-5 days another bud rather suddenly (within 10-12 hours) appeared This was repeated several times with a new bud often at the top of the last one (Fig 4 a-e)

11 weeks after operation, when amphotericin was withdrawn the exudate in the left



Fig 2
Case 1 O D The granulomes in the vitreous body composed of granulocytes and macrophages Htx – eosin × 220

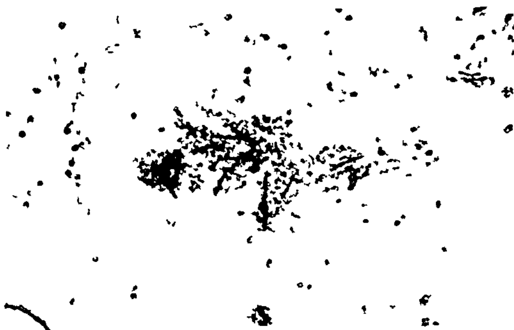


Fig 3
Case 1 O D The hyphae of Aspergillus fumigatus in the granulomes Gomori methanamine silver stain × 220

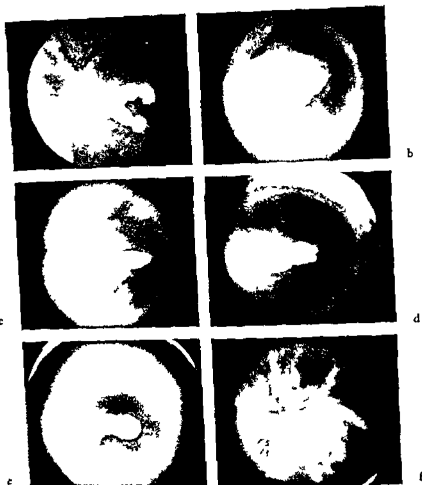


Fig 4
Case 9 O S Photographs taken on the following days after operation
a) 60 b) 66 c) 0 d) 7 e) 78 f) 140

vitreous body protruded + 15 D and the eye ground could not be distinguished (Fig 4 e) Visual acuity was reduced to observation of hand movements and the visual field showed a large central scotoma

At that time 600 units nystatin suspended in 0 15 cc 0 9 % saline was injected into the left vitreous body 4 hours after the injection there was a marked pericorneal hyperaemia aqueous flare and the vitreous body was completely clouded Visual acuity was reduced to percept on. Topical atropin and prednisolon were instilled

The reaction in the anterior parts of the eye gradually diminished and 3 weeks later when the vitreous body had cleared a retinal detachment could be seen in the lower

half of the eye ground The vitreous mass had retracted and no budding was observed after the injection

4 years later the cornea lens and vitreous body were clear and a retinal detachment remained in the lower and temporal part and white scars covered the optic disc and the macula (Fig 4 f) Intraocular pressure was 20 mmHg (*Schiot*) During the first ° years the patient had been able to register movements of the hand in the lower part of the visual field but later she almost lost light perception in this eye

O D The right eye also showed budding of the exudate in the eye ground but the progress was slow and the lesion was mainly localized to the retina (Fig 5 a-b) No new »buds were seen 1–2 weeks after the injection of nystatin into the left eye and

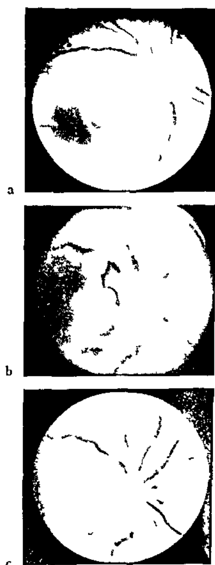


Fig 5

Case 2 O D Photographs taken on the following days after operation a) 60 b) 91 c) 127

then the exudate decreased. Four years later a scar involved the disc and the macula and caused a central scotoma (Fig 5 c) Intraocular pressure was 16 mmHg (*Schiot*) Visual acuity was 0 1–0.2

Case 3

Clinical history A 5? year old woman in whom parts of oesofagus and ventricle were resected because of a low differentiated squamous cell carcinoma got post operative fever which was treated with large doses of antibiotics (penicillin, chloramphenicol cloxacillin and ampicillin) Three weeks after the operation Candida albicans was cul tured from blood Antibacterial therapy was then withdrawn and amphotericin B 20 mg/day was given for 7 weeks with a few days interruption because of chills and nausea.

Five weeks after the first operation the patient was reoperated and an incarcerated liverlobulus was resected. She again received large doses of antibiotics and because of shock and electrolyte deficiency hydrocortison was given intravenously for 10 days (total dose 1500 mg) Her condition improved and half a year later her general health was rather good.

Eye signs 4 weeks after the first operation the patient noticed blurring of the vision. One week later examination of the eyes showed slight cloudiness of the vitreous body slight oedema of the papilla and engorgement of the veins There were several small white rounded cotton wool exudations and a few streak haemorrhages in the central part of the eye ground The lesions gradually diminished (Fig 6) except for a temporary increase of an exudate during the period when intravenous hydrocortison had been gi en. Three months later the patient complained of no eye symptoms visual acuity O D = O S = 1 0 All lesions in the eye ground had disappeared except for an in active scar in O D

Case 4

Clinical history A 4? year old woman with Mb Crohn, severely ill because of a perfo ration of colon sigmoid was operated twice 1 st a colostomy and 4 weeks later colec



Fig 6
Case 3 O D Photography taken ? months after 1 st operation.

half of the eye ground The vitreous mass had retracted and no budding was observed after the injection

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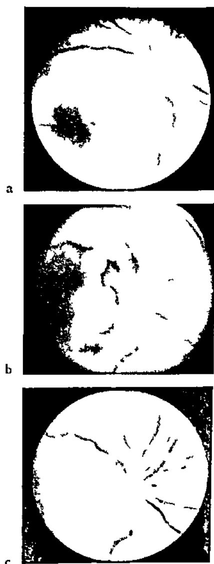


Fig 5

Case 2 O D Photographs taken on the following days after operation a) 60 b) 91 c) 127

then the exudate decreased Four years later a scar involved the disc and the macula and caused a central scotoma (Fig 5 c) Intraocular pressure was 16 mmHg (*Schiot*) Visual acuity was 0 1–0 ⁹

Case 3

Clinical history A 52 year old woman in whom parts of oesofagus and ventricle were resected because of a low differentiated squamous cell carcinoma got post operative fever which was treated with large doses of antibiotics (penicillin chloramphenicol cloxacillin and ampicillin) Three weeks after the operation Candida albicans was cul tured from blood Antibacterial therapy was then withdrawn and amphotericin B 20 mg/day was given for 7 weeks with a few days interruption because of chills and nausea.

Five weeks after the first operation the patient was reoperated and an incarcerated liverlobulus was resected. She again received large doses of antibiotics and because of shock and electrolyte deficiency hydrocortison was given intravenously for 10 days (total dose 1500 mg) Her condition improved and half a year later her general health was rather good

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Case 4

Clinical history A 42 year old woman with Mb Crohn, severely ill because of a perfo ration of colon sigmoid was operated twice 1 st a colostomy and 4 weeks later colec



Fig 6
Case 3 O D Photography taken 2 months after 1 st operation

tomy + partial resection of ileum + ileostomy During this time she was treated with antibiotics (penicillin ampicillin cloxacillin and oxytetracycline) and cortison (hydro cortison intravenously 4050 mg/3 weeks and prednisolon orally 220 mg/2 weeks)

6 weeks after the first operation Candida albicans was cultured from blood Anti biotics were then exchanged for amphotericin B and prednisolon withdrawn within one week Amphotericin B was given intravenously for 6 weeks (total dose 1637 mg) The patient s general condition improved

Eye signs When candida was cultured from the blood the eyes were examined the anterior parts were normal but in each eye ground a small white hard exudate was localized near macula In O D the exudate enlarged during the following 3 weeks and extended into the vitreous body (Fig 7) However during the next months it diminished leaving a small scar in the retina and a small opacity in the vitreous body

O S The exudate was smaller and diminished within 1 month

Discussion

Embolism to the retina from mycotic endocarditis has been reported twice [1,2] In the second of these reports Aspergillus fumigatus was involved It is of special interest that in the last reported case as well as in this case the uveitis was the first clinical sign leading to the suspicion of a fungal infection In this case the suspicion lead to specific antimycotic therapy given in spite of negative blood cultures

In cases 2–4 Candida albicans was cultured from the blood and the clinical signs agreed with a Candida endophthalmitis [3,4] It is probable that the peculiar buds observed in the second case are typical for fungus infection

It has been suggested that the increase of fungal infections during the last decade is due to the increased use of antibiotics and corticosteroids In the 4 cases reported here heavy doses of antibiotics had been given and in 3 of them also



Fig 7

Case 4 O D Photography taken 2½ months after 1st operation

steroids Furthermore in 2 cases there seemed to be a progress of the infection specially during the time when amphotericin therapy was combined with steroid therapy This is in agreement with previous opinions[6] that corticosteroids even combined with antifungal drugs are contraindicated in the treatment of fungal infection

Amphotericin B treatment has been successful in several cases of fungus infection[1] During this treatment the third and the fourth case improved but in the first case the drug was probably given too late In the second case amphotericin treatment was probably not sufficient and this may be due to poor penetration into the intraocular fluids

Amphotericin and nystatin have been injected intraocularly in animals[7] and a few humans[8,9] The substances are rather toxic in high doses The present injection of 600 units nystatin stopped the progress of infection However there was a temporary intense reaction following the injection but at least 4 years afterwards there were no opacities in the cornea lens or anterior vitreous body As a remnant of the abscess in the vitreous body however there was a large scar which covered the optic disc and macula and caused a traction detachment Because of these changes it was not possible to decide if the bad function was due to the fungus abscess or a toxic effect of the injected substance

Summary

4 cases with metastatic spread of fungus infection to the eye are presented In one case with Aspergillus fumigatus endophthalmitis the diagnosis was confirmed by culture from and by microscopic examination of the eye In one case with *Candida albicans* endophthalmitis nystatin was injected into the vitreous body

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ACTA OPHTHALMOLOGICA VOL 49 1971

From the Eye Clinic University of Helsinki
(Head Professor Salme Vannas M D)

DIAGNOSIS OF UNILATERAL EXOPHTHALMOS WITH SPECIAL REFERENCE TO PNEUMO ORBITOTOMOGRAPHY

BY

J A CASTRÉN A VANNAS & C J SJÖBLOM

An etiological diagnosis in cases of unilateral exophthalmos often requires a considerable number of examinations before it can be decided whether an inflammation endocrine disturbance some rare disease or a tumour requiring surgery is involved

For tumour diagnosis proper the following methods are available in addition to the routine ophthalmological studies neurological examination and certain laboratory tests

1 Conventional roentgenological study of the orbit
2 Orbital tomography
3 Orbitotomography using a positive or negative contrast medium (gas)
4 Orbital phlebography
5 Carotid angiography
6 Ultrasonic examination of the orbit
7 Biopsy
8 Steroid trial

A so called orbital pseudotumour that is a non specific inflammation in the orbital tissues is involved fairly frequently It can be verified by taking a biopsy specimen The condition can be cured as a rule by steroid therapy which may be administered also in the diagnostic sense in cases of exophthalmos of ambiguous etiology

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We present here a short survey of the methods listed and the material from our clinic for which these methods of investigation were employed

Material and methods

We went over all the cases undergoing pneumo orbitotomography at our clinic in 1960–1969 There were 27 patients in all five men and 22 women A total of 40 pneumotomographies were performed on these patients

Conventional roentgen examination of the orbit without contrast medium was carried out on all the patients before orbitotomography Nine patients underwent carotid angiography after pneumotomography In one case pneumoencephalography was also undertaken as it was assumed that the tumour had spread to both the orbit and the cranial cavity

Conventional roentgenography of the orbit According to the literature (*Beisner* 1969) routine roentgenography reveals changes in about 50 per cent of the cases of unilateral exophthalmos Special exposures of the optic foramen are often usefull in assessing the situation

Skull roentgenograms were taken in the posterio anterior and lateral projections Special foramen opticum exposures were also made in 21 cases

Orbitotomography It is probably rarely that this reveals a soft tissue tumour of the orbit unless changes have been demonstrated in the conventional roentgenography of the orbit. However this method of examination may perhaps be indicated before undertaking more laborious investigations which may involve risks of complication Tomographic techniques have been improved and by using linear or especially hypocycloid movement very thin sections can be focused (*Yamagisawa et al* 1968)

Orbitotomography with negative contrast medium At least air oxygen and carbon dioxide have been used in roentgenography The first publication on this subject dates from 1927 (*Stauning & Herrenschwandt*) Resorption of air from the orbit takes about five days but oxygen disappears in roughly 24 hours and carbon dioxide even faster The amounts of gas and the injection technique used vary

Only one case of complication in connection with pneumo orbitotomographies has been reported It involved a hemangioma and an air embolus entered the brain The patient lost consciousness and developed hemiplegia but recovered in 20 min (*Dollfus* 1953)

In our series 14–30 cc of air was injected into the posterior part of the orbit after routine premedication (1 mg of pethidinechloride kg) The injection was initially performed relatively rapidly and strongly (*Keskey Letsch* 1956) but later slowly At the end the needle was drawn outwards from the orbit and 6–8

cc of additional air was injected right beside the posterior wall of the eyeball to aid good visualisation of the posterior part of the eyeball Tomographs were then made at intervals of 5 mm in both the posterio anterior and lateral pro jections If the patient s proptosis was increased so that it was not possible to close the eye properly an antibiotic ointment was administered and the eye was covered with a gauze patch The patients spent *1–2 days in hospital for the in* tervention A child aged 15 months was examined under general anesthesia

Orbitophlebography This method appears to be excellent in theory Contrast medium (usually Urografin 60 %) is injected into the angular vein or frontal vein and passes into the orbital veins which are then visualised In practice however it is difficult to perform the injection properly and contrast medium readily enters the subcutaneous space Contrast medium may also flow into the wrong vessels and this makes it difficult to interpret lateral exposures

Carotid angiography With 35 % diodrast the ophthalmic artery is visualised *poorly but it is seen in 98 per cent of the cases when the now commonly used* 60 % Urografin is injected Injection of 10 ml of concentrated triiodates into the internal carotid artery brings out even ophthalmic artery branches which are 0 3 mm in diameter (*Beisner* 1969)

Complications occur occasionally from angiograhpies but they are rarely serious At least one fatality and one case of blindness have been reported (*Beisner* 1969)

Eight cc of 60 % Urografin was injected into the common carotid artery of our patients Roentgenograms were made in the frontal plane for three seconds at two exposures per second and then at one per second in all 12 roentgeno grams

Ultrasonic study of the orbit Retrobulbar tumours can be diagnosed in addi tion to intraocular tumours by the ultrasonic method of examination (*Baum & Greenwood* 1960) The investigation is safe but the apparatus is fairly expen sive Ultrasonic *examination (University Eye Clinic Turku Finland)* was per formed on one patient

Results

Pneumo orbitotomography gave a positive finding in nine of the 27 cases (Fig 1) It was confirmed operatively in seven of the patients There was one case in which a positive finding was made twice the second time *after recurrence of* the tumour five years later (Table I)

The positive result given by pneumo orbitotomography could not be verified in two cases In one of them the tumour that was considered with fair certainty to be present was not operated (No 25) since it grew very slowly and the pa



Fig 1

Pneumotomographs of the orbital spongioblastoma (Case no 1) Lines indicate the tumour (a) and bulbus (b) which have been visualised clearly

Table 1

The results of various roentgenographical studies and the patient s diagnosis
+ pathological finding — normal finding or no definite pathological change

Patient number	Age Years	Pneumo orbitoto mography	Carotisan giography	Other x ray examina tions	Diagnosis
1	1 5	+		—	orbital spongioblastoma
2	7	—		+	spongioblastoma of the optic nerve
3	10	—	—	—	residival orbital lymphangioma
		—			
	11	+			
	16	+			
4	15	+		—	orbital neurinoma
5	23	+	+	—	orbital meningeoma
6	24	+		+	mixed tumour of the lacrimal gland
7	24	—		—	orbital pseudotumour
8	25	—	—	—	orbital pseudotumour
9	28	—	—	—	orbital pseudotumour
		—			
10	28	—		—	juxtapapillar chorioditis
		—			
		—			
11	37	—		—	orbital pseudotumour
12	40	—		—	orbital pseudotumour
13	41	—		—	orbital pseudotumour
14	41	—		—	paralysis of the oculomotor nerve exopthalmos
		—			

15	45	—	—	—	orbital pseudotumour
16	46	+	—	—	orbital tumour ?
17	50	—	—	+	orbital pseudotumour
18	51	—		—	exophthalmos mucocele of the frontal sinus
19	54	— —	— —	—	orbital hemangioma
20	54	— — —	—	—	metastatic sarcoma exophthalmos
21	54	+		+	epidermoid carcinoma of the middle ear and orbital metastases
22	55	+ +		+	recidival maxillar carcinoma
23	55	—		—	orbital pseudotumour
24	57	— —		—	nodular autonomic goiter unilateral exophthalmos
25	72	+ +		—	orbital tumour
26	77	—		—	orbital pseudotumour
27	80	—		—	orbital pseudotumour

tient was already 72 years of age and refused surgery In the other one (No 16) Naffziger s operation was performed in 1969 but nothing indicative of a tu mour was found The patient continues however to attend for a follow up as the exophthalmos has increased gradually even postoperatively For suspicion of pseudotumour the patient was given a course of steroid therapy but without avail Carotid angiography gave a normal finding in this case Orbitophlebo graphy was also performed but the result was difficult to interpret

Pneumotomography of the orbit was negative twice although the subsequent operation revealed that one of the patients had hemangioma and the other spon gioblastoma Even carotid angiography which was performed twice failed to yield a diagnosis in the case with hemangioma (No 19) It was reached only at explorative surgery necessitated by the increasing exophthalmos The patient with spongioblastoma (No 2) was only seven years of age so pneumo orbitoto mography was not repeated despite the small quantity of air Pneumoencephalo graphy revealed tumour expansion also behind the orbit. The optic foramen was also distinctly enlarged on the side of the tumour The results were verified at operation

Carotid angiography was performed on nine patients The finding at pneumo tomography and carotid angiography was mainly the same positive or negative (Table 1) Pneumo orbitotomography was positive and carotid angiography ne




Fig 1
Pneumotomographs of the orbital spongioblastoma (Case no 1) Lines indicate the tumour (a) and bulbus (b) which have been visualised clearly

Table I
The results of various roentgenographical studies and the patient s diagnosis
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	11	+			
	16	+			
4	15	+		—	orbital neurinoma
5	23	+	+	—	orbital meningeoma
6	24	+		+	mixed tumour of the lacrimal gland
7	24	—		—	orbital pseudotumour
8	25	—	—	—	orbital pseudotumour
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		—			
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12	40	—		—	orbital pseudotumour
13	41	—		—	orbital pseudotumour
14	41	—		—	paralysis of the oculomotor nerve exopthalmos
		—			

patient had had a radical ear operation for epidermoid carcinoma two years earlier Only one case of complication of a similar type has been reported in the literature (*Dollfus* 1953)

Carotid angiography of the patient with lymphangioma revealed nothing pathological whereas pneumotomography disclosed the presence of a toumour According to *Krauenbuhl* (1958) the value of angiography is in fact primarily that it is capable of demonstrating the pathological vasculature of a space consuming lesion and not so much the displacement of the ophthalmic artery and its branches

A special case was a patient who had already had Naffziger s operation twice without any tumour being discovered However as pneumo orbitography revealed a distinct tumour behind the eyeball a third operation was undertaken and a neurinoma almost the size of the eyeball was removed A detailed report of this case was published in 1961 (*Castren*) This case showed that even operative exploration cannot always be trusted

According to the results we also concluded that a pseudotomur very often in 40 per cent in this material is the cause of unilateral exophthalmos

Summary

The material consisted of 27 patients with unilateral exophthalmos aged from 15 months to 80 years They all underwent orbital pneumotomography some of them several (2–4) times Forty pneumotomographies in all were performed The results of these investigations were compared with those obtained by other methods of examination (conventional roentgenography and orbitotomography carotid angiography) Pneumoencephalography phlebography or ultrasonic study were also performed occasionally

An orbital tumour was verified at operation in a total of eight cases One additional patient revealed changes due to carcinoma that had been operated and irradiated earlier Furthermore there was one probable tumour which was not treated by surgery

Orbital changes were demonstrated by conventional roentgenography in a half of these cases Pneumotomography gave a positive finding in nine cases

Carotid angiography gave the same result as pneumotomography in seven cases In one case the angiography was negative but the pneumotomography finding gave the impression of a tumour However *no tumour was detected at* operation.

In one case (orbitallymphoma) on the other hand angiography gave a normal finding but the pneumotomography finding was positive

A rare transient complication caused by the *injection of air* is described The

gative in two cases One of the two patients (No 16) has already been described and the other (No 3) was found on operation to have lymphangioma which had not been visualised in carotid angiography

Conventional roentgenographies displayed pathological changes in five cases A tumour was verified operatively in four of these patients The changes established were either an enlarged optic foramen or degenerative osseous changes There was one instance in which an enlarged optic foramen was demonstrated roentgenographically also in connection with pseudotumour

Ultrasonic examination of the orbit was done in one case (No 4) The finding was a suspected tumour

Discussion

For orbital pneumotomography the necessary apparatus is available and thus is no obstacle to this method of examination The patients need only premedication not anesthesia However general anesthesia must be employed with small children The procedure is easy to carry out and the hospitalisation period is short The examination can be repeated after a few days and the risk of complications is slight The investigation was repeated mostly because the quantity of air in the posterior orbit was too small and the contrast was poor Air had leaked in these cases into the anterior parts of the orbit and the lids owing to inadequate positioning of the needle or perhaps too fast injection When the volume of air is 38 cc or less there is no danger to life and the investigation can be performed on old persons and children

Pneumotomographs are sometimes difficult to interpret and the work calls for experience and practice Usually however the tumour was beautifully outlined If there is too little air in the orbit the examination should be repeated as was frequently done by us

Positive contrast media may also be used in orbitotomography but they often disappear poorly from the tissue and irritate it There are observations in the literature about spasms of the central artery and optic atrophy in connection with this intervention (*Lombardi* 1967)

There was only one instance of complications from injection of air in our own material The patient lost consciousness for a few seconds approx a minute after the injection and horizontal nystagmus was seen at the same time The patient subsequently spoke haltingly for 10 min The heart rate remained good throughout The patient had difficulties in swallowing and pyrexia for a week afterwards The pyrexia was attributed to central causes Roentgenograms revealed that air had entered the subdural space below the frontal lobe There were also profuse osseous changes in the orbital wall but no distinct defect The

From the Department of Ophthalmology University of Helsinki
(Head Prof Salme Vannas M D)

LATE RESULTS OF SURGERY ON EYES WITH PRIMARY GLAUCOMA AND CATARACT

BY

LEILA LAATIKAINEN

The coexistence of cataract and chronic open angle glaucoma or chronic angle closure glaucoma is increasing with the increasing average age of the population The cataract accelerating effect of some antiglaucomatous drugs such as phospholine iodide had also been discussed in recent years (*Axelsson & Holmberg* 1966 *Tarkkanen & Karjalainen* 1966) However there is no general agreement on the surgical procedure in eyes with glaucoma and beginning or advanced cataract. Three different approaches can be considered

1 A primary antiglaucomatous operation has been advocated by several authors in eyes with uncontrolled glaucoma (*Elschnig* 1922 *Guyton* 1945 *François* 1947 *Kirby* 1950 *Ramsay* 1950 *Stallard* 1950 *Arruga* 1952 *Leydhecker* 1954) But it is widely held that glaucoma operations often hasten the progress of cataract (see *Sugar* 1970) In addition malignant glaucoma may develop after a filtering operation especially in cases of chronic angle closure glaucoma. Lens extraction after a filtering operation requires a special technique in order to avoid the bleb Therefore superior corneal (*Gasteiger* 1949 *Leydhecker* 1954 *Zenker* 1958 inferior limbal (*François* 1947) or temporal limbal section (*Sugar* 1965) has been recommended

2 Lens extraction has been performed as the primary operation by many surgeons especially in glaucomatous eyes in which the tension can be normalized with miotics (*Elschnig* 1922 *Vannas M* 1934 *Guyton* 1945 *Gasteiger*

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ease of performance of pneumotomography, its diagnostic significance and safety have been emphasised

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From the Department of Ophthalmology University of Helsinki
(Head Prof Salme Vannas M D)

LATE RESULTS OF SURGERY ON EYES WITH PRIMARY GLAUCOMA AND CATARACT

BY

LEILA LAATIKAINEN

The coexistence of cataract and chronic open angle glaucoma or chronic angle closure glaucoma is increasing with the increasing average age of the population The cataract accelerating effect of some antiglaucomatous drugs such as phospholine iodide had also been discussed in recent years (*Axelsson & Holmberg* 1966 *Tarkkanen & Karjalainen* 1966) However there is *no general* agreement on the surgical procedure in eyes with glaucoma and beginning or advanced cataract. Three different approaches can be considered

1 A primary antiglaucomatous operation has been advocated by several authors in eyes with uncontrolled glaucoma (*Elschnig* 1922 *Guyton* 1945 *François* 1947 *Kirby* 1950 *Ramsay* 1950 *Stallard* 1950 *Arruga* 1952 *Leydhecker* 1954) But it is widely held that glaucoma operations often hasten the progress of cataract (see *Sugar* 1970) In addition malignant glaucoma may develop after a filtering operation especially in cases of chronic angle closure glaucoma. Lens extraction after a filtering operation requires a special technique in order to avoid the bleb Therefore superior corneal (*Gasteiger* 1949 *Leydhecker* 1954 *Zenker* 1958 inferior limbal (*François* 1947) or temporal limbal section (*Sugar* 1965) has been recommended

2 Lens extraction has been performed as the primary operation by many surgeons especially in glaucomatous eyes in which the tension can be normalized with miotics (*Elschnig* 1922 *Vannas M* 1934 *Guyton* 1945 *Gasteiger*

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ease of performance of pneumotomography its diagnostic significance and safety have been emphasised

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occasionally with capsule forceps Pilocarpine and eserine were instilled upon the eye or acetylcholine was injected into the anterior chamber (*Castren & Lis tola* 1970) An air bubble was usually placed into the anterior chamber

Cataract extraction after a filtering operation The technique was largely the same as for regular cataract extraction Because of the bleb the preplaced triangular suture was not used in all cases The knife incision was made in front of the bleb and shorter than in the regular cataract extraction. Several additional sutures were used in most cases

Postoperative management On the first postoperative days the pupil was dilated after the disappearance of the air bubble Steroid drops were usually instilled from the third day on Sometimes Diamox® in doses of 125 mg three to four times daily was given postoperatively

In 91 per cent of all cases extraction could be done intracapsularly

Results

Group A Cataract extraction following glaucoma surgery

An antiglaucomatous operation before lens extraction had been performed on 32 eyes 20 of these had chronic open angle glaucoma which was classified in six as capsular glaucoma, while 12 had chronic angle closure glaucoma Lens extraction was performed 2 months to 20 years (mean 6 years) after glaucoma surgery The average follow up period was 2 3 years the minimum (2 cases) being 8 months

Open angle glaucoma The mean age of the patients at the time of lens extraction was 72 2 years Iridencleisis or peripheral iridencleisis was performed on 13 eyes cyclodialysis on 6 eyes and both operations on one eye

Before glaucoma surgery the intraocular pressure was not controlled in any of the eyes After the operation the pressure was 20 mmHg or less in 15 eyes and 11 of these eyes required no antiglaucomatous medication (Tables I and II)

Cataract extraction usually had no effect on intraocular pressure In 16 eyes the pressure continued at 20 mmHg or less 13 of these eyes required no medication (Tables I and II) In altogether 7 eyes antiglaucomatous medication had to be resumed 2 weeks to 1 year after cataract extraction

In only one eye was loss of a functioning fistula seen after cataract extraction and in this case cyclodialysis had to be performed 20 months later In three other eyes filtration failure was observed even before cataract extraction

Two eyes with previous cyclodialysis and one eye with previous iridencleisis were hypotonic (T<10) after lens extraction

1949 *Ramsay* 1950 *Lee & Weih* 1950 *Kirby* 1950 *Nonay* 1953 *Sugar* 1951 *Tuovinen* 1961 *Vorosmarthy & Ballschuh* 1968) In such cases cataract extraction alone has often normalized or at least reduced the intraocular pressure However it is held by many authors that cataract extraction alone rarely results in a permanent lowering of intraocular pressure (*Galin et al* 1961) If the beneficial effect of cataract surgery is insufficient and the pressure cannot be controlled medically some glaucoma operation can be done later

3 A combined operation for glaucoma and cataract has been recommended by *many surgeons during the past twenty years* Cataract extraction has been combined with sclerectomy (*Wright* 1937 *Lee & Weih* 1950 *Kuchle* 1962) iridencleisis (*Lee & Weih* 1950 *Birge* 1952 *Wenaas & Sterl bach* 1955 *Sarda et al* 1968) sclerectomy with iris inclusion (*Hughes* 1959 *Birge* 1966 *Scuderi & Cardia* 1967) cyclodialysis (*Boberg-Ans* 1964 *Harrington* 1966 *Galin et al* 1969) and sclerectomy with diathermy (*Bangerter* 1963 *Stocker* 1964 *MacLean* 1964 *Vannas S* 1969 *Maumenee & Wilkinson* 1970) A prolonged flat anterior chamber was reported as the most disturbing complication of the combined operation especially after iridencleisis

This investigation was carried out in order to study the effect of cataract extraction on the intraocular pressure in glaucomatous eyes both after conservative treatment and after antiglaucomatous operation

Material and the operative technique

The study comprised 98 glaucomatous eyes on which lens extraction was performed in the years 1960–1968 Cases with a short follow up period (less than 6 months) were excluded In 32 eyes some kind of antiglaucomatous surgery had been performed before the cataract operation whereas in 66 eyes cataract extraction *was the primary procedure*

Regular cataract extraction In order to lower the intraocular pressure Diamox® was usually used preoperatively combined with Mannitol infusion if necessary The operation was usually done under local anaesthesia with facial akinesia (*O Brien and/or van Lint*) An upper corneal knife incision with a preplaced triangular corneoscleral suture was used in all these cases (*Vannas M* 1949) The length of the knife incision was determined by the depth of the anterior chamber The incision was lengthened both nasally and temporally with scissors After two peripheral iridotomies two appositional sutures of either Barraquer s silk or rat tail suture were placed on each side of the triangular suture Enzymatic zonulolysis with alphachymotrypsin was usually used Extraction was performed with a cryo extractor or earlier with an erisiphake and

cular degeneration and in one eye postoperative epithelial invasion explained the poor vision

Characteristic glaucomatous visual field losses graded principally as proposed by *Tarkkanen* (1962) were found to be as follows Normal central and peripheral fields were found in 10 cases grade I (slight enlargement of the blind spot) in 3 cases grade II (a large Bjerrum scotoma and/or a marked nasal step) in 4 cases and grade III (a large quadrant defect of up to 10 degrees at least from the point of fixation or even more extensive defects) in 3 cases

Chronic angle closure glaucoma The mean age of the patients was 61.1 years Iridencleisis or peripheral iridencleisis was performed in 10 eyes and peripheral iridectomy in 2 eyes before cataract extraction

After glaucoma surgery the pressure was well controlled in 9 eyes in 5 of these eyes without any medical treatment After cataract extraction the pressure remained within normal limits in 10 eyes in 5 of these without drugs In the other 2 eyes the need for antiglaucomatous medication was almost unchanged and treatment had to be begun 2 weeks to one year after cataract extraction (Tables III and IV)

Loss of a functioning fistula was not found in any of these eyes

Central visual acuity after cataract extraction was 0.5 or better in 9 eyes (75 per cent) In the other three eyes the main cause for decreased visual acuity was considered to be macular degeneration in two cases and bullous keratopathy in one case

Large glaucomatous visual field defects (grade II and III) were only found in one eye and slight changes (grade I) were detected in 3 eyes

Table III

Chronic angle closure glaucoma Intraocular pressure after separate glaucoma and cataract operations

T	No of cases		
	Preoperative	after glaucoma operation	after cataract extraction
≤ 10	–	2	–
11–20	–	7	10
21–26	–	2	2
> 26	12	1	–
Total	1	12	12

Table I

Open angle glaucoma Intraocular pressure after separate glaucoma and cataract operations

T	No of cases		
	Preoperative	after glaucoma operation	after cataract extraction
≤ 10	– (–)*)	1 (–)*)	3 (–)*)
11–20	– (–)	14 (3)	13 (5)
21–26	4 (1)	3 (1)	3 (1)
> 26	16 (5)	2 (2)	1 (–)
Total	20 (6)	20 (6)	20 (6)

*) Cases of capsular glaucoma

Table II

Open angle glaucoma Medical therapy before and after separate glaucoma and cataract operations

Drugs**)	No of cases		
	Preoperative	after glaucoma operation	after cataract extraction
None	– (–)*)	11 (1)*)	13 (3)*)
M	9 (1)	3 (1)	2 (–)
M+E	3 (1)	4 (3)	– (–)
M+D	6 (3)	– (–)	1 (–)
M+E+D	2 (1)	2 (1)	4 (3)
Total	20 (6)	20 (6)	20 (6)

*) Cases of capsular glaucoma
**) M=miotics E=epinephrine D=acetazolamide

Central visual acuity after cataract extraction was 0 5 or better in 10 eyes (50 per cent) In the other 10 eyes with decreased visual acuity glaucoma was considered to be the main cause in 5 cases (25 per cent) whereas in 4 eyes ma

cular degeneration and in one eye postoperative epithelial invasion explained the poor vision

Characteristic glaucomatous visual field losses graded principally as proposed by *Tarkkanen* (1962) were found to be as follows Normal central and peripheral fields were found in 10 cases grade I (slight enlargement of the blind spot) in 3 cases grade II (a large Bjerrum scotoma and/or a marked nasal step) in 4 cases and grade III (a large quadrant defect of up to 10 degrees at least from the point of fixation or even more extensive defects) in 3 cases

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Table III

Chronic angle closure glaucoma Intraocular pressure after separate glaucoma and cataract operations

T	No of cases		
	Preoperative	after glaucoma operation	after cataract extraction
≤ 10	-	2	-
11–20	-	7	10
21–26	-	2	2
> 26	12	1	-
Total	12	12	12

Table IV

Chronic angle closure glaucoma Medical therapy before and after separate glaucoma and cataract operations

Drugs*)	No of cases		
	Preoperative	after glaucoma operation	after cataract extraction
None	–	5	5
M	7	5	5
M+D	5	2	2
Total	12	12	12

*) M=miotics D=acetazolamide

Group B Cataract extraction without previous glaucoma surgery

In 66 glaucomatous eyes cataract extraction was done as the primary operation There were 60 eyes with chronic open angle glaucoma 18 of which had capsular glaucoma and 6 eyes with chronic angle closure glaucoma The follow up period was 6 months (4 cases) to 20 years (mean 3 years) so that postoperative hypotension after lens extraction should have subsided

Open angle glaucoma The mean age of patients at the time of cataract extraction was 72 5 years In spite of medication the intraocular pressure was poorly controlled in 28 eyes before lens extraction compared to 12 eyes after the operation (Table V)

The type of medical therapy before and after cataract operation is seen in Table VI In 8 eyes glaucoma was diagnosed when the patients were admitted to hospital for cataract operation the others had miotics epinephrine or acetazolamide either alone or in various combinations After cataract operation 29 eyes (ca 50 per cent) required no medication and in addition in 14 eyes the need for antiglaucomatous medication had diminished Five eyes however required more effective treatment after cataract extraction than preoperatively and on one eye cyclodialysis was done 8 years after lens extraction Of the 18 eyes with capsular glaucoma 7 (39 per cent) required no treatment after lens extraction in 5 eyes the control of glaucoma became easier postoperatively and in the remaining 6 eyes the antiglaucomatous medication was unchanged

Central visual acuity after cataract extraction was 0 5 or better in 47 eyes (78 per cent) As in the first group causes other than glaucoma could be found to account for the decreased visual acuity in many cases In 6 eyes the decrease

Table V

Open angle glaucoma Intraocular pressure before and after cataract extraction

T	No of eyes	
	before	after
≤ 10	— (—)*)	3 (1))
11–20	32 (10)	45 (15)
21–26	21 (6)	10 (1)
> 26	7 (2)	2 (1)
Total	60 (18)	60 (18)

) Cases of capsular glaucoma

Table VI

Open angle glaucoma Medical therapy before and after cataract extraction

Drugs)	No of eyes	
	before	after
None	8 (4))	29 (7)*)
M	33 (10)	15 (8)
M+F	4 (1)	5 (1)
M+D	4 (1)	6 (1)
E and or D	3 (—)	2 (1)
M+E+D	8 (2)	3 (—)
Total	60 (18)	60 (18)

) Cases of capsular glaucoma
) M=miotics E=epinephrine D=acetazolamide

was principally due to macular degeneration and only in 7 eyes (12 per cent) to glaucoma

Visual field losses were found as follows grade I 6 cases grade II 4 cases and grade III 5 cases

Table IV
Chronic angle closure glaucoma Medical therapy before and after separate glaucoma and cataract operations

Drugs*)	No of cases		
	Preoperative	after glaucoma operation	after cataract extraction
None	–	5	5
M	7	5	5
M+D	5	2	2
Total	12	12	12

*) M=miotics D=acetazolamide

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In 66 glaucomatous eyes cataract extraction was done as the primary operation There were 60 eyes with chronic open angle glaucoma 18 of which had capsular glaucoma and 6 eyes with chronic angle closure glaucoma The follow up period was 6 months (4 cases) to 20 years (mean 3 years) so that postoperative hypotension after lens extraction should have subsided

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11-20	32 (10)	45 (15)
21-26	21 (6)	10 (1)
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) Cases of capsular glaucoma

Table VI

Open angle glaucoma Medical therapy before and after cataract extraction

Drugs)	No of eyes	
	before	after
None	8 (4))	29 (7))
M	33 (10)	15 (8)
M+E	4 (1)	5 (1)
M+D	4 (1)	6 (1)
E and or D	3 (—)	2 (1)
M+E+D	8 (2)	3 (—)
Total	60 (18)	60 (18)

) Cases of capsular glaucoma
) M=miotics E epinephrine D=acetazolamide

was principally due to macular degeneration and only in 7 eyes (12 per cent) to glaucoma

Visual field losses were found as follows grade I 6 cases grade II 4 cases and grade III 5 cases

Chronic angle closure glaucoma There were only six eyes with chronic angle closure glaucoma in which no glaucoma surgery was done before cataract extraction The mean age of these patients at the time of cataract extraction was 58 5 years Some lowering of the intraocular pressure level could be seen in 3 of these eyes although the need for medical treatment only decreased in two eyes In two eyes cyclodialysis was done about five years after cataract extraction (Tables VII and VIII)

Table VII
Chronic angle closure glaucoma Intraocular pressure before and after cataract extraction

T	No of eyes	
	before	after
≤ 10	–	
11–20	3	4
21–26	–	2
> 26	3	–
Total	6	6

Table VIII
Chronic angle closure glaucoma Medical therapy before and after cataract extraction

Drugs*)	No of cases	
	before	after
None	–	2
M	2	2
M+D	4	2
Total	6	6

*) M=miotics D=acetazolamide

Central visual acuity after cataract extraction was 0.5 or better in two eyes and in these cases the visual fields were also normal In two eyes decreased central visual acuity and visual field defects were caused by retinitis pigmentosa In the other two eyes glaucoma was considered to be the cause of decreased visual acuity

Discussion

At the time of cataract extraction the mean age of the patients with open angle glaucoma was almost the same (72 2 and 72 5 years) in the groups A and B so that in most cases no clear relationship between filtration surgery and cataract formation could be found in this study However in five of the 20 eyes treated operatively for open angle glaucoma the period between the two operations was only 2 months to 1 5 years indicating that filtration surgery may have accelerated the cataract in these eyes In all these five eyes there were already some lens opacities at the time of filtration surgery but mature cataract had developed 3 weeks to one year after the operation No complications were detected during the glaucoma operation In one eye delayed formation of anterior chamber and postoperative hypotension may have accelerated the development of cataract but in the other eyes no special causes for cataract development could be found The postoperative cataract formation has been regarded as an important cause for visual deterioration following filtration surgery (*Tarkkanen & Eskelin* 1970)

In cases of chronic angle closure glaucoma the mean age of the patients at the time of cataract surgery was higher in the group A where an antiglaucomatous operation was done than in the group B where cataract extraction alone was performed However in these eyes too the cataract accelerating effect of filtration surgery could be suspected in some cases because in three eyes a mature cataract developed within one year after filtration surgery In all these three cases the formation of anterior chamber was delayed and postoperative hypotension occurred

In the eyes where glaucoma had previously been treated by filtration surgery (group A) cataract extraction by upper corneal incision usually had no effect on the intraocular pressure level In only one of the total of 32 eyes was it necessary to perform a further antiglaucomatous operation because of loss of filtration after lens extraction These results indicate that cataract extraction though more difficult can be done after filtration surgery without damage to the filtering bleb

In the group B cataract extraction alone resulted in an obvious lowering of intraocular pressure in about 40 per cent of the eyes with open angle glaucoma

This beneficial effect on glaucoma control was most clearly seen in eyes treated with miotics alone preoperatively. The postoperative values of visual fields seem to indicate that there were fewer serious cases of open angle glaucoma in the group B than in the group A where separate glaucoma and cataract operations were performed. In cases of capsular glaucoma the beneficial effect of lens extraction on the need for medical therapy was less obvious than in the other eyes with open angle glaucoma.

In milder cases of open angle glaucoma lens extraction alone seems to control or, at least, to help the control of the intraocular pressure while in more serious cases of open angle glaucoma and in most cases of chronic angle closure glaucoma this effect is not sufficient. In these eyes a combination of some antiglaucomatous procedure with lens extraction seems indicated, especially if multiple operations on old persons are to be avoided, as may be imperative in some cases because of the delicate general health of the patients. Follow up studies of such a combined operation for glaucoma and cataract in our hospital are in progress and will be reported separately.

Summary

The effect of lens extraction on intraocular pressure in glaucomatous eyes was studied. The material comprised 98 glaucomatous eyes operated on for cataract in the years 1960–1968 in the University Eye Clinic, Helsinki.

In cases with previous antiglaucomatous surgery lens extraction had no distinct effect on the intraocular pressure or on the need for antiglaucomatous medication. Only in one eye was loss of filtration found postoperatively.

In cases where cataract extraction was the primary procedure the beneficial effect on glaucoma control was seen in about 70 per cent of eyes with open angle glaucoma. In 50 per cent of eyes with open angle glaucoma the pressure was adequately controlled without any postoperative medication. In the more difficult cases of chronic open angle glaucoma and in most cases of chronic angle closure glaucoma the effect of lens extraction alone seems insufficient to control the glaucoma.

The cataract accelerating effect of filtration surgery is discussed.

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From the Helsinki University Eye Hospital
(Head Professor Salme Vannas M D) Helsinki Finland

RETINOBLASTOMA IN FINLAND 1912–1964

BY

AHTI TARKKANEN & ERKKI TUOVINEN

The present study is based on a series of retinoblastoma patients diagnosed in Finland within a period from 1912 to 1964 A complete accumulation of cases was attempted for the assessment of relative frequencies of retinoblastoma during the period of study The data were primarily intended for cancer demographers for the construction of incidence rates of retinoblastoma in various parts of the world Furthermore as it has been suggested by *Davies* (1967) that retinoblastoma might be used as an index cancer to which the frequency of other cancers might be compared special efforts to bring this cancer to light in different countries should be made

Material and methods

The material consists of 171 patients from 1912 to 1964 which were collected by hunting through the archives of pathological laboratories and eye departments of the country The work was alleviated by the finding that the great majority of the cases had been seen in two different eye departments the Helsinki University Eye Hospital sharing the major portion After 1954 the archives of the Finnish Cancer Registery were also employed Enquiries were also sent to the patients and their families to elucidate the familial occurrence of retinoblastoma Blocks or sections were received of 107 cases These were restudied

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mainly for the evaluation of the cellular characteristics of retinoblastoma cases encountered in Finland

Results

General considerations The distribution of cases according to sex and age at which the tumour was diagnosed (Table I) reveals that 86 per cent of the cases had been diagnosed before the age of 4 years and that both sexes were almost equally effected The youngest patient was aged 3 weeks and the oldest 7 years

The tumour was bilateral in 29 per cent and in unilateral cases the right and the left eyes were affected in equal fashion (Table II) The cardinal presenting signs have been listed in Table III with the amaurotic cat s eye and squint constituting the principal signs

Prognosis Follow up data were available of 133 cases (Table IV) These were compiled as cumulative data listing the period in years from enucleation to the last follow up All cases were followed for at least two years or to death There were 93 unilateral cases with an over all survival rate of 70 per cent whereas of the 40 bilateral cases only 30 per cent had survived It has to be emphasized however that in the series treated during the late stages of the period study i e 1958–1964 far better survival rates were observed

The histopathological characteristics of the 107 tumours revealed that 77 (72 per cent) of the cases showed definite rosettes There was however no signifi

Table I

Distribution according to sex age of 171 patients with retinoblastoma at the time of diagnosis

Age	Males	Females	Total	Percent of total
2 weeks to 11 months	16	19	35	21
1 year to 1 11/12 years	25	18	43	25
2 years to 2 11/12 years	19	27	46	27
3 years to 3 11/12 years	10	13	23	13
4 years to 4 11/12 years	5	7	12	7
5 years to 7 years	5	7	12	7
	80	91	171	100

Table II

Analysis of 171 cases of retinoblastoma according to unilateral or bilateral involvement and affected side

Unilateral	Right	54
	Left	67
		121
Bilateral		50
	Total	171

Table III

Cardinal presenting sign in 136 patients with retinoblastoma

Sign	No of cases	Per cent of total
White pupillary reflex	73	54
Strabismus	24	18
Unilateral dilated pupil	5	4
Heterochromia	1	
Routine examination	1	1
Decreased vision	12	8
Inflammation	20	15
	136	100

cant relationship between the grade of differentiation and the mortality rate between these groups

The length of the past history has been compiled in Table V It is evident that in cases where there has been a delay before the treatment had been started a poor prognosis was found i.e. 18 of the 20 cases with past history over 12 months had died whereas the mortality rate is around 20 per cent in cases with the past history up to 6 months

Incidence There were 15 cases (11 per cent) who were close relatives to each other representing 7 families Among them one father and a daughter with retinoblastoma was found as well as one mother and a daughter These were

Table IV
Cumulative follow up Time in years from enucleation to follow up

Years	Unilateral		Bilateral	
	Alive	Dead	Alive	Dead
2	20	28	6	21
3	7		1	2
5	12		3	3
10	13		1	2
20	10		1	
≥ 25	3			
	65	28	12	28
Total 133				

Table V
Length of the past history Prognostic consideration

Length of the past history	No of cases	Fatal cases
0– 1 months	36	9
1– 3 months	34	5
3– 6 months	24	6
6–12 months	28	12
over 12 months	20	18
Total	142	50

the only cases representing two generations the remaining cases being siblings

The frequency of new retinoblastoma cases from 1912 through 1964 has been compiled in Table VI The frequency has been expressed as the ratio new cases compared to the number of live births in consecutive five year periods A distinct increase in the frequency has taken place during the period of observation The low figures during the early periods may be explained by assuming that some cases have escaped our survey

Table VI

The frequency of retinoblastoma in Finland The number of new cases compared to the number of live births

Period	Frequency
1915–1919	1 89 000
1920–1924	1 68 000
1925–1929	1 38 000
1930–1934	1 32 000
1935–1939	1 30 000
1940–1944	1 19 000
1945–1949	1 23 000
1950–1954	1 17 000
1955–1959	1 16 000
1960–1964	1 16 000

If however two different 15-year periods are compared namely 1925–1939 with a frequency 1 33000 against 1950–1964 with a frequency 1 16000 a definite increase has taken place

To illustrate the frequency of retinoblastoma in Finland the data were compared with the available statistics from some other countries (Table VII) It appears that the frequency of retinoblastoma in Finland has been of the same magnitude during the same periods in Denmark Norway and Holland From

Table VII

Comparison of the frequency of retinoblastoma in different countries

Period	Country	Frequency
1958–1961	Denmark	1 19 000
1958–1961	Finland	1 21 000
1953 1960	Norway	1 17 000
1953 1960	Finland	1 16 000
19[illegible] –1955	Holland	1 14 000
195[illegible] –1955	Finland	1 14 000
1939–1956	Ireland	1 [illegible]7 000
1939–1956	Finland	1 19 000

Table IV

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	Alive	Dead	Alive	Dead
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Frequency data on the incidence of retinoblastoma in different populations have been reviewed by *François* (1964) *Schappert Kimmijser et al* (1966) and *Vogel* (1967) In all populations examined so far the present incidence of retinoblastoma seems to be somewhat less than 1 20 000 births The increase of the incidence over the period 1925–1957 has been estimated by *François* (1964) to be roughly 11 × 10^{-4} In Holland the morbidity of retinoblastoma amounted to 1 34 000 for the years 1927–1929 whereas a similar survey for the years 1952–1955 revealed a morbidity of 1 14 700 Interestingly enough when the familial cases were excluded from the calculations a frequency of 1 16 000 was found Our data (Tables VI and VII) support the opinion of the increase of the incidence of retinoblastoma The frequency in the Finnish population seems to be equal to those reported from other countries

Summary

From 1912 to 1964 171 patients with retinoblastoma were diagnosed in Finland The frequency was calculated as the ratio new cases compared to the number of live births for consecutive five year periods A definite increase of the frequency of retinoblastoma has taken place From 1925 to 1939 a frequency of 1 33 000 was obtained while from 1950 to 1964 the frequency was 1 16 000 The frequency was compared with available data from some other countries The frequency of retinoblastoma in Finland seemed to be equal with that reported from Denmark Norway and Holland A positive family history was obtained in 11 per cent The material has been analyzed in detail with regard to sex and age prognosis cardinal presenting signs and histopathological characteristics Prolonged duration of symptoms before treatment was directly related to the case fatality Only two patients had survived out of the twenty cases with duration of symptoms over 12 months

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1938 to 1956 however the frequency of retinoblastoma in Finland was 1 19 000 whereas in Ireland 1 27 000

Discussion

In our series 86 per cent of the cases were diagnosed before the age of 4 years (Table I) This agrees well with the observations of *Taktikos* (1966) In his material of 287 patients approximately 87 per cent were younger than 4 years Modest majorities of male patients with retinoblastoma have been reported earlier (*Bech & Jensen* 1961 *Carbajal* 1958 *Herm & Heath* 1956) In the series of *Leelawongs & Regan* 1968 however altogether 32 of the 52 patients were males This is the opposite to our material with a slight preponderance to females (91 out of 171) Bilateral involvement of retinoblastoma in different materials has varied from 30 to 59 per cent The figures of *Carbajal* (1958) and *Jensen* (1965) around 30 per cent agree well with our 28 per cent *Lommatsch* (1970) observed bilateral involvement in 59 per cent while of the 1/60 cases on file in the Registry of Ophthalmic Pathology 19 3 per cent were known to be bilateral (*Zimmerman* 1969)

The survival figures in our series 70 per cent of the unilateral and 30 per cent of the bilateral cases are lower than in other series In the study reported by *Carbajal* (1958) the corresponding figures were 80 and 50 per cent and in that of *Jensen (1965)* 86 and 55 per cent It has to be emphasized that the number of survivors is rather high among the cases dating from the later period of the study A ten year review of the results of treatment is in preparation It is of interest that the number of tumours forming rosettes in our study 72 per cent agrees with the reports of *Carbajal & Jensen* The degree of the differentiation of the tumour however is of doubtful prognostic significance as was already shown by *Taktikos* (1966)

The duration of the symptoms appears to bear a direct relationship to the case fatality *Carbajal* (1958) showed that the fatality rate was less when the duration of symptoms before treatment was two weeks to six months than when duration was more prolonged Similarly the mean lapse between recognition and treatment was 16 4 months among fatal cases and 5 38 months among survivors (*Pieroni et al* 1969) In our study only two patients had survived out of the twenty cases with the duration of symptoms over 12 months

A positive family history was obtained in 11 per cent of our cases This figure is the same as in the series reported by *Pieroni et al* (1969) *Carbajal* (1958) recorded family history in 41 per cent It is likely that the familial incidence will increase with the years due to higher survival and marriage rates It does not however account for the increase of the incidence of retinoblastoma

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Reprint request to

Ahti Tarkkanen M D
Helsinki University Eye Hospital
Haartmaninkatu 4 C Helsinki 29
Finland

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From the Eye department
Aalborg Sygehus 9000 Denmark

THE FREQUENCY OF RUBEOSIS IRIDIS IN DIABETIC PATIENTS

BY

VAGN OHRT

The frequency of rubeosis in diabetes mellitus is stated very differently in various studies ranging from less than 0 5 per cent up to 10 per cent (cf table 1)

Caird et al (1969) still consider rubeosis to be a rare diabetic manifestation occuring in less than 1 per cent of diabetics He arrives at this conclusion by considering the frequency of malignant diabetic retinopathy" as this condition is present in most cases in which rubeosis is found

What exactly accounts for this great variation in the different statements is *not easily understood The studies date from the last 15 years during which*

Table 1
The frequency of rubeosis found in earlier investigations

Authors	Diabetic patients	No of rubeosis	Percentage
Palomar Palomar 1956	416	23	55
Jahnert et al 1957	3750	14	0.37
Armstrong 1960	393	1	0 25
Streiff 1963	3 6	25	6 7
Ohrt 1 6	404	41	10
Armaly et al 196	211	2	1

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period the percentage of long-term diabetics (duration of more than 15 years) with whom rubeosis occurs has changed only very little. The most likely explanation are differences in pigmentation of the iris in the various series Thus a dense pigmentation may completely conceal the development of abnormal vessels in the early stages which constitute the majority of the cases

In his investigation from 1967 the author found rubeosis to be a rather frequent manifestation but 10 per cent was probably too high a figure as the long term diabetic patients constituted too large a percentage (39 per cent) of the total material Thus the purpose of this study is to present a diabetic material which constitutes a better basis for the evaluation of the frequency of rubeosis

Material

The material comprising 309 diabetics is taken from a private ophthalmologic clinic and biomicroscopy as well as ophthalmoscopy were performed in all cases with *known diabetes If the patients were examined more* than once only the results of the first examination have been registered It has been collected throughout 9 years and constitutes 1 3 per cent of the total number of patients of 23 500 from that period Tables 2 and 3 show distribution according to sex age and duration of the disease

Ophthalmoscopy could be performed in 293 cases diabetic retinopathy was found in 130 patients or 42 per cent Table 4 shows the distribution of retinopathy according to severity

Table 2

Age and sex distribution of the diabetic patients

Age in years	Men	Women	Total
–29	13	17	30
30–39	8	7	15
40–49	17	24	41
50–59	26	33	59
60–69	33	65	98
70–	21	45	66
Total	118	191	309

Table 3

Distribution of the patients according to the duration of diabetes

Duration in years	Men	Women	Total
0–4	41	85	126
5–9	24	37	61
10–14	17	22	39
15–19	14	18	32
20–	22	29	51
Total	118	191	309

Table 4

Distribution of diabetic retinopathy according to severity

Type of lesion	No	Percentage of all cases of retinopathy	Percentage of all diabetics
ML	16	12	5
H	38	29	12
H + E	48	37	16
Prol	28	22	9
Total	130		

ML Minimal lesion one or two sanguinolent spots
H Haemorrhages – H + E Haemorrhages + typical diabetic exudates
Prol Proliferation of vessels and connective tissue

The Occurence of Rubeosis in the Series

Rubeosis was found at the first examination in 21 patients 11 men and 10 women or 6 8 per cent of the total number of diabetic patients The distribution according to age and duration of the disease is shown in table 5

Sixteen of the 21 cases with rubeosis were bilateral In 26 eyes (18 patients) the development of the abnormal vessels was found in an early stage present only in the annulus minor varying from a few vessels peripupillary to vessels

Table 5

Distribution of rubeosis according to the age and the duration of diabetes

Age in years	No	Duration in years	No
–29	3	0– 4	5
30–39	–	5– 9	–
40–49	6	10–14	–
50–59	5	15–19	3
60–69	5	20–	13
70–	2		
Total	21		21

all along the circumference whereas abnormal vessels were not yet present in the periphery or the chamber angle

Haemorrhagic glaucoma had developed in 4 eyes in 3 patients at the first examination Retinopathy was found in all 37 eyes with rubeosis in 28 eyes (18 patients) in the malignant form with proliferative retinal changes

Rubeosis is found in 16 per cent of all cases with retinopathy and in 64 per cent of the patients with proliferations in the retina

As to the material it should moreover be mentioned that approximately half of the patients were examined more than once – most of them within comparatively short periods of time and amongst these haemorrhagic glaucoma developed in 3 more eyes in 3 patients rubeosis appeared in 7 other patients – all having proliferative retinopathy – and spontaneous disappearance of the rubeosis vessels was seen in 8 eyes in 6 patients Thus it would not be possible to answer the question as to how many of the diabetics either had had rubeosis or developed it later on during the period of investigation

Discussion

It is not easy to provide a representative material of diabetic patients who can be subjected to biomicroscopy Even though diabetic patients most often consult the ophthalmologist for the same reasons as other patients many of them come only because of their diabetes first of all the long term diabetics and especially those with more severe and symptomrendering eye changes One would there

fore expect from the material presented in this article that the percentage of dia betic patients would be greater than in the population in general and further more a preponderance of long term diabetics and cases with diabetic retino pathy especially in its most severe form

The diabetics in this material constitute as mentioned 1 3 per cent of the total number of the patients The prevalence of verified diabetes in Denmark probab ly lies between 0 5 per cent and 1 per cent. *Horstmann* in 1949 stated 0 47 per cent for a Danish locality (the town of Odense) and *Lundbæk* (1953) estimated a frequency of 0 61 per cent for the town of Aarhus An investigation from the United States from 1969 states a frequency of known diabetes of as much as 14 5 per 1000

The 27 per cent made up by the long term diabetics in this series can be com pared with the statement from 1953 by *Lundbæk* who found that between one fourth and one fifth of the diagnosed diabetics in Aarhus (with a population of 114 344 in 1950) were long term diabetics

The frequency of diabetic retinopathy in this series of 46 per cent may be compared with those found in some large recent investigations *Aarseth* (1953) 42 per cent *Kornerup* (1955) 46 8 per cent *Jahnert et al* (1957) 33 per cent and *Caird et al* (1969) 36 8 per cent

Finally a comparison may be made between the frequency of proliferative retinopathy of 9 per cent of the total number of diabetics in this material and the following findings *Aarseth* (1953) found this form in 3 3 per cent *Lund bæk* (1953) in 6 3 per cent *Engelson* (1954) in 6 9 per cent *Jahnert* et al (1957) in 2 6 per cent *Kornerup* (1958) in 8 4 per cent and *Burditt et al* (1968) in 2 per cent of their diabetic patients

Thus the figures in this series show a slightly higher representation of diabe tics in the total number of patients than could be expected in the population Furthermore the frequency of proliferative retinopathy found in the present material exceeds the corresponding figures of comparable series However the differences are so small that the material as a whole may be considered repre sentative of a Danish population and serve as a basis when evaluating the fre quency of rubeosis – with due regard to the slight divergence From the 6 8 per cent found in this study the frequency of rubeosis in a representative diabetes material can be estimated to about 5 per cent

However it is more relevant to evaluate the frequency of rubeosis from the number of cases of proliferative retinopathy with which it is intimately con nected Calculated in this way it was 64 per cent, as already mentioned In the other diabetes material presented by the author in 1967 the corresponding figure was 48 per cent. If the two materials are added together abnormal vessels in the irides were found in 48 of the 93 patients with proliferations in the re tina, viz. 5? per cent However there was a total of 61 rubeosis patients in the two series as in 5 cases ophthalmoscopy could not be performed and in 8 cases

no proliferation of vessels and connective tissue in the retina could be demonstrated

Based on these figures one may generally conclude that about half of all the patients with proliferative retinopathy at a given time have rubeosis as well However as a smaller number of patients with rubeosis but without proliferations must be added the frequency of rubeosis can be estimated to about 60 per cent of the number of proliferative cases found in a diabetes material whether this is representative or not

Summary

In a series comprising 309 diabetic patients rubeosis at the first examination was found in 21 patients or 6 8 per cent Due to the nature of the material a slight correction has to be made and hereafter the frequency is estimated to be about 5 per cent in a representative Danish diabetes material

As however rubeosis is closely connected with proliferative retinopathy it is more relevant to consider the frequency in this connection and rubeosis was found in 64 per cent of these patients When this series is added to the series presented earlier by the author one finds a number of cases with rubeosis (61) which is high enough to justify the general conclusion that about half of all the patients with proliferative retinopathy at a given time have rubeosis However rubeosis is also seen in a smaller number of patients with retinopathy but without proliferations Therefore one arrives at the final conclusion that the frequency of rubeosis in a diabetes material can be considered to be about 60 per cent of the number of the proliferative cases in the series

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Equipments material and method of research

The ultrasonic equipment used was Kretztechnik s model 7000 and the trans ducers unfocused crystals of 6 MHz/8 mm and 10 MHz/5 mm. The amplification control of the equipment was fit with a db scale During the examination two amplifications were used i e db reserves 40 and 20 The ultrasonic apparatus was equipped with a Tektronix oscilloscope with which echo amplitudes were measured

At the examinations I used newly slaughtered pig eyes which were prepared by removing all parts outside the bulbus The eyes were placed in a bowl of water on a stand made of thin copper wire The transducer was also fixed to a stand and immersed in the bowl above the eye. The sound was reflected by a steel ball with a diameter of 1.5 mm. The ball was moved below the eye and it was used for the examination of such cross sections of the sound field as lay 1 mm apart from one another The distance between the transducer and the steel ball was always kept at 30 mm and that between the posterior surface of the eye and the steel ball 5 mm At all examinations control measurements were first made in plain water At the control measurements the db reserve was set at 40 When the examination was made from different directions through the lens the db reserve was either 40 or 20 When the examination was made through the eye but past the lens the db reserve was always 40

The examinations were made in the following situations

1 The eye was placed on the stand so that the sound beam travelled axially through the eye. At this examination two different transducers were used i e. 6 MHz/8 mm and 10 MHz/5 mm 2 The eye was placed on the stand with the equatorial area straight up The sound beam travelled through the lens but at right angles against the anatomical axis of the eye 3 The eye was placed so that the sound beam travelled through the lens but hit the axis of the eye at a 45° angle 4 The eye was placed so that the equatorial area was on top and the sound beam travelled through the eye but past the lens At examinations 2 3 and 4 a transducer of 6 MHz/8 mm was used Each examination was carried out with 5 different eyes The echoes reflected by the steel ball produced echo amplitude curves which lay 1 mm from one another The amplitudes of these curves are directly proportionate to the sound pressures at the corresponding points of the field

Results

The results obtained at various examinations were all very homogeneous and could easily be repeated

From the Ophthalmic Department of the University Hospital Turku Finland (Head Prof Arvo Oksala)

EXPERIMENTAL STUDIES ON THE EFFECT OF THE EYE GLOBE ON THE ULTRASONIC FIELD*)

BY

ARVO OKSALA

The attenuation of ultrasound in a live tissue is primarily caused by absorption reflection refraction and scattering Experimental and clinical observations have shown that the lens attenuates ultrasound quite strongly and diverges the sound beam (*Oksala & Blok* 1968) If the sound passes perpendicularly through the surface of the eye only slight attenuation takes place in the sound field (*Oksala & Hakkinen* 1968) When the sound travels slantingly through the surface of the eye attenuation increases and at a 70° angle of incidence even a total reflection can be observed (*Oksala & Hakkinen* 1969)

In a earlier paper (*Oksala & Varonen* 1965) I have studied the effect of the whole eye on the sound field by measuring the changes in respect to water in the echo amplitude curves of one cross section of the sound field at 4 different distances This investigation was made both axially through the lens and diasclerally past it The results showed that at an axial examination the lens strongly attenuates ultrasound and at the same time diverges the sound beam At a diascleral examination the eye had only a slightly attenuating effect on ultrasound

In this paper I shall study the effect of the eye globe on the sound field by examining several cross sections of the sound field and measuring the effect when the sound beam travels through the lens from various directions or diasclerally past the lens

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Equipments material and method of research

The ultrasonic equipment used was Kretztechnik s model 7000 and the trans ducers unfocused crystals of 6 MHz/8 mm and 10 MHz/5 mm. The amplification control of the equipment was fit with a db scale During the examination two amplifications were used i e. db reserves 40 and 20 The ultrasonic apparatus was equipped with a Tektronix oscilloscope with which echo amplitudes were measured

At the examinations I used newly slaughtered pig eyes which were prepared by removing all parts outside the bulbus The eyes were placed in a bowl of water on a stand made of thin copper wire The transducer was also fixed to a stand and immersed in the bowl above the eye The sound was reflected by a steel ball with a diameter of 1.5 mm. The ball was moved below the eye and it was used for the examination of such cross sections of the sound field as lay 1 mm apart from one another The distance between the transducer and the steel ball was always kept at 30 mm and that between the posterior surface of the eye and the steel ball 5 mm At all examinations control measurements were first made in plain water At the control measurements the db reserve was set at 40 When the examination was made from different directions through the lens the db reserve was either 40 or 20 When the examination was made through the eye but past the lens the db reserve was always 40

The examinations were made in the following situations

1 The eye was placed on the stand so that the sound beam travelled axially through the eye At this examination two different transducers were used i e. 6 MHz/8 mm and 10 MHz/5 mm 2 The eye was placed on the stand with the equatorial area straight up The sound beam travelled through the lens but at right angles against the anatomical axis of the eye 3 The eye was placed so that the sound beam travelled through the lens but hit the axis of the eye at a 45° angle 4 The eye was placed so that the equatorial area was on top and the sound beam travelled through the eye but past the lens At examinations 2 3 and 4 a transducer of 6 MHz/8 mm was used Each examination was carried out with 5 different eyes The echoes reflected by the steel ball produced echo amplitude curves which lay 1 mm from one another The amplitudes of these curves are directly proportionate to the sound pressures at the corresponding points of the field

Results

The results obtained at various examinations were all very homogeneous and could easily be repeated

1 Fig 1 presents the results obtained with the 6 MHz/8 mm transducer at an axial examination At the bottom (right) one can see the control curves in water The low echo amplitude curves in the centre were obtained through the whole eye and the lens with the same amplifications as in the control examination i e db reserve = 40 On top (left) one can see 2 sets of echo amplitude curves obtained from the same situation with a db reserve = 20

The control curves were very regular in shape and the diameter of the sound field at the examined point was 7 mm When the examination was made through the eye and the lens with a db reserve = 40, the lens was observed to attenuate ultrasound strongly and also to diverge the sound beam When the db reserve was 40 the diameter of the sound beam was 9 mm If the amplification was increased to a db reserve value 20 the sound beam widened to 13 mm and the echo amplitude curves grew very irregular The curves showed several maxima

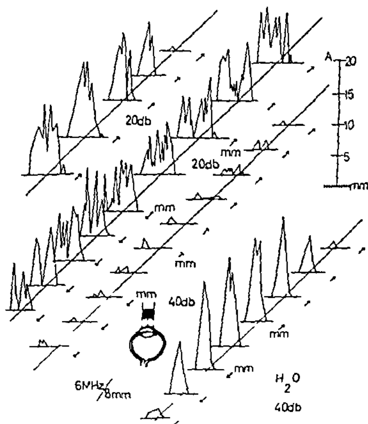


Fig 1
The effect of the whole eye on the ultrasonic field when the sound beam travelled axially through the eye with a 6 MHz/8 mm transducer

and minima and fairly high maxima could be measured in an area which was as much as 12 mm wide. When a transducer of 10 MHz/5 mm was used at an axial examination the echo amplitude curves presented in *Fig 2 were obtained* Bottom right one can again see the control curves The attenuation of ultrasound at the higher frequency was so great that with a db reserve = 40 no echoes from the steel ball could be observed The echo amplitude curves on the left were measured with a db reserve = 20 The diameter of the sound beam widened from the 4 mm of the control curve to 9 mm The whole eye affected the sound field by producing a lot of maxima and minima. Fairly high maxima were measured in a 5 mm wide area.

2 Fig 3 represents the results when the sound beam travelled through the anterior parts of the eye and at right angles against the axis of the eye. Bottom right one can see the regularly shaped control curves The curves in the center show the effect of the eye on the sound field with the same amplification as in

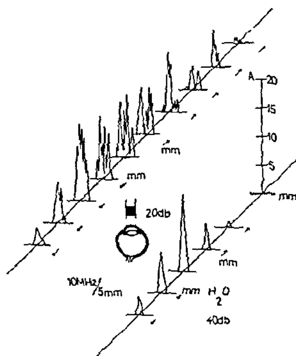


Fig 2
The effect of the whole eye on the sound field when the sound beam travelled axially through the eye with a 10 MHz 5 mm transducer

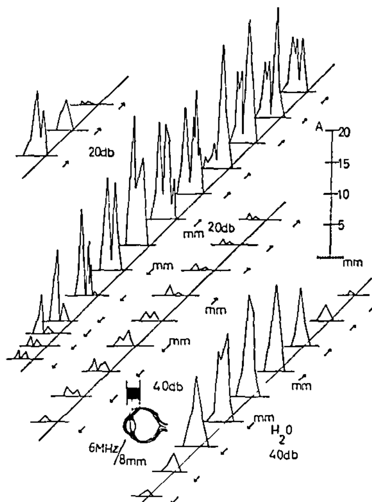


Fig 3
The results of an examination where the sound beam pierced the anterior parts of the eye and travelled at right angles against the axis of the eye

the control curves The two sets of curves on the left present the effect of the eye on the sound field with a db reserve = 20

At the control examination the width of the sound beam was 8 mm and like wise when the examination was made with the same amplification through the lens When however the db reserve was 20 the width of the sound beam was 15 mm after travelling through the eye and the lens At an examination which was made with the higher amplification through the eye high maxima and small minima could be measured in a 10 mm wide area

3 Fig 4 represents echo amplitude curves obtained at an examination through the eye and the lens when the sound beam hit the axis of the eye at a 45° angle. On the right one can see the control curves and in the center the effect of the

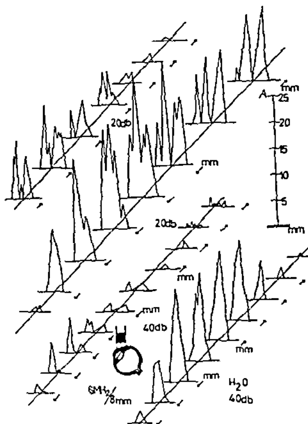


Fig 4
The results of an examination where the sound beam travelled through the anterior parts of the eye and at a 45° angle against the axis of the eye

eye on the sound field with the same amplification The two sets of curves top left represent the effect with a db reserve — 20 The width of the sound beam at the control examination was 8 mm. With the same amplification the attenuating effect of the eye was considerable even if the diameter of the sound beam remained almost the same i e 9 mm With the higher amplification the diameter of the beam was 14 mm and strong maxima and minima were obtained in a 10 m wide area.

4 *Fig 5 represents the results when the sound beam travelled through the eye but past the lens* On the right one can see the control curves and on the left the effect of the eye on the sound field After the sound has pierced the surface

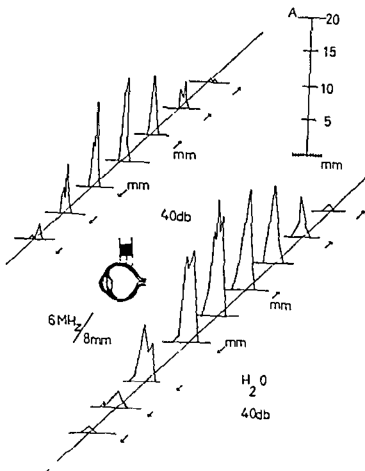


Fig 5
The sound beam has travelled through the eye but past the lens

of the eye twice the beam becomes slightly narrower i e from 8 to 6 mm and the sound is also a little attenuated but the curves stay fairly regular in shape

Discussion

The results now obtained are coherent with earlier experimental observations in that the whole eye and the lens strongly attenuate ultrasound and divert the sound beam At earlier examinations the measurements were however made at one cross section of the sound field only

The results show that ultrasound becomes strongly attenuated when examinations are made from various directions through the lens If this attenuation is compensated by a considerable increase in amplification which is necessary for the registration of echoes one has to examine with a sound beam which is approximately twice as wide as the beam right in front of the transducer The effect of the lens also makes the echo amplitude curves irregular with their maxima and minima

When the examination is made through the whole eye but past the lens the sound beam becomes a little narrower The shapes and amplitudes of the echo amplitude curves are however similar to the ones obtained in water

When one thinks of the possible clinical significance of these experimental results one should notice that as the lens strongly attenuates ultrasound and diverts the sound beam it makes the analysis of echograms more difficult both in A and B scans The impeding effect of the lens can best be seen at a B scan examination of the orbit where one can observe distortion in the picture as well as artifact echoes In order to be able to register enough sufficiently high echoes one has to use fairly high amplification which however widens then the irregular sound beam Intraocular diseases should be examined past the lens and orbital diseases also past the eye, as far as possible

Summary

Pig eyes were used for the experimental examination of the effect of a whole eye on the sound field when the sound beam travelled through the lens from three different directions and diasclerally through the whole eye but past the lens The lens always caused strong attenuation in the sound field and a divergence in the sound beam. In addition distinct maxima and minima appeared in the sound field When the examination was made through the whole eye but past the lens only a slight change took place in the sound field The examination of eye and orbital diseases should always also be made past the lens and the eye

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The Department of Experimental Ophthalmology
University Eye Clinic Lund Sweden

PUPILLARY FLOW IN THE WATER PROVOCATION TEST

BY

O WIEBERT

Introduction

The water provocation test seems to be one of the most commonly used tests for establishing the diagnosis of glaucoma simplex in suspect cases (For an extensive survey see Leydhecker 1) The test is performed by giving a large quantity of water – usually 1000 ml – to the fasting patient An intraocular pressure increase follows the water ingestion as a rule It generally reaches its maximum after 30 min A rise surpassing 10 or 8 mm Hg (the critical value varies with different authors) supports the glaucoma diagnosis

The pressure increase is attributed by most authors to an increased production of aqueous Others have found (*Ballantine* 2 *Becker et al* 3) an increased outflow resistance in a considerable percentage of the patients

Stepanik (4) noted in pathologically reacting cases an increase in both flow and resistance in the negative cases only an increased resistance.

The results mentioned have been obtained by tonographic technique

The aim of the present investigation was in the first place to measure directly the pupillary flow and especially the time course of the flow This is possible to outline since a number of consecutive flow values can be obtained The relation between the courses of the pressure and the flow has a considerable interest, since conclusions concerning changes in the outflow resistance might be drawn These changes may also have a bearing on pressure regulation problems

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Method

The pupillary aqueous flow has been measured according to the principle given by *Holm & Krakau* (5) The details of the method are described by *Holm* (6) In short the content of the anterior chamber is stained with fluorescein from outside with the aid of iontophoresis It is possible to see the newly formed aqueous emerging from the pupil, standing out as a clear bubble against the green coloured chamber content The volume of the vesicle can be measured photographically, by a sort of optical sectioning This is done on two occasions about 10 secs apart. A flow value is calculable from the volume difference obtained The measurement can be repeated after mixing the chamber content by eye movements

As a rule four or five separate determinations (x_i) and the mean values calculated (m_j) are made on each occasion

The pupil has to be miotic and therefore the normals have been given 2 per cent pilocarpine three times daily for three days before the flow measurements The glaucomatous patients remained on their miotic therapy (pilocarpine)

The intraocular pressure was determined applanatorically according to Goldmann

The investigation was started in the morning with the patient fasting since the previous evening After determination of the IOP four series of flow values ($m_1 - m_4$) were made each comprising four or five separate determinations (x_i) The intervals between the determinations x_i was 30–45 secs and a pause of about 10 min was made between each sequence After the 4th series the IOP was determined again

Then 14 ml/kg bodyweight water was given in a period of 5 minutes (7) Fifteen minutes after the water consumption a new series of flow measurements was made followed by an IOP determination This was repeated every 15 minutes during a period of 90 minutes In some cases when the coloration of the aqueous was insufficient the measurements of flow could only be made for as long as 60 minutes

Only one eye was measured on each occasion Except for some irritation in the eye during the day of examination the patients had no complaints

Material

Group I Glaucoma simplex 12 eyes The IOP at least once recorded higher than 24 mm Hg Open chamber angle in all cases Four cases had visual field defects Surgery in no cases

Group II Glaucoma suspects 13 eyes The IOP on several occasions 22–24 mm Hg Open chamber angle no visual field defects

Group III Normals 9 eyes Ophthalmoscopy biomicroscopy gonioscopy and perimetry normal

Group IV Controls 8 eyes These eyes fall in the group glaucoma suspects The flow examination was made as in the other cases but no water was given

All patients fall in the range 45 to 70 years of age

Results

The IOP as could be expected showed an increase the maximum of which appeared at the first measuring point (after 15 min) in the normal group and at 30 min in the other groups (This difference is not significant) The increase was pathological (≥ 8 mm Hg) in four cases only This may be attributed to the fact that the patients were still on pilocarpine drops when the test was made The maximum mean increase was 2 5 in the normal 3 7 in the suspect and 3 1 mm Hg in the glaucoma group

After 90 minutes the pressure was almost normal in the normal group and 1 mm above normal in the glaucoma group In the control group without water there was an IOP decrease by nearly 1 mm from the beginning to the end of the experiment.

The flow values in the three groups before water was not correlated to the pressure values The pressure is naturally as a rule higher in the glaucomatous groups than in the normal one whereas the flow values are scattered in a similar range for all groups

The flow was increased in all but 4 cases after water The increase was significant on the 97 5 per cent level or better (t test) in 47 per cent of the cases In the control series where no water was given there was an increase in 5 of 8 cases one of them was significant on the 95 per cent level

The individual courses vary some start rapidly and fall soon, other increase slowly As has been described by *Holm & Wiebert* (8) there is a considerable variation in the individual flow values Partly this is due to methodological errors but to a considerable extent it is caused by variation in the amount of fluid passing the pupil Whether the latter variation represents a true variation in aqueous formation or is only the result of strain in the extraocular muscles etc has not yet been established Anyhow this variation hampers a detailed analysis of the separate curves and it must be an open question whether there is an increased outflow resistance or not (Some of the experiments could be interpreted in this way) However the mean curves of the three groups take a very similar course (Fig 1–3 Tab V) Since the flow level varies in the range 0 4–3 9 mm³

Method

The pupillary aqueous flow has been measured according to the principle given by *Holm* & *Krakau* (5) The details of the method are described by *Holm* (6) In short the content of the anterior chamber is stained with fluorescein from out side with the aid of iontophoresis It is possible to see the newly formed aqueous emerging from the pupil standing out as a clear bubble against the green co loured chamber content The volume of the vesicle can be measured photogra phically, by a sort of optical sectioning This is done on two occasions about 10 secs apart. A flow value is calculable from the volume difference obtained The measurement can be repeated after mixing the chamber content by eye move ments

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Material

Group I Glaucoma simplex 12 eyes The IOP at least once recorded higher than 24 mm Hg Open chamber angle in all cases Four cases had visual field defects Surgery in no cases

Table II
Glaucoma Suspects

Pat	Before water			IOP	After water			Max change in IOP	Change in F_p	Significance of change in F_p
	F_p	N	S e		F_p	N	S e			
KO	1 4	16	0 2	18 0	1 7	16	0 2	2 0	+ 21 %	0
ANi	2 2	24	0 1	17 0	3 2	15	0 3	3 0	+ 45 %	+
LH	1 8	12	0 2	21 0	3 1	24	0 2	4 0	+ 72 %	+
HO	2 0	18	0 2	23 0	2 8	24	0 1	11 0	+ 40 %	+
KS	2 3	16	0 2	17 0	3 2	22	0 2	3 0	+ 39 %	+
HO	1 0	16	0 1	22 0	1 4	18	0 1	6 0	+ 40 %	+
UN	1 6	17	0 3	20 5	[illegible]	27	0 3	4 5	+ 19 %	0
AIW	2 1	19	0 2	19 0	2 7	25	0 2	4 0	+ 29 %	0
BA	1 6	18	0 3	21 0	3 2	[illegible]	0 4	2 5	+ 100 %	+
UA	0 7	17	0 1	16 0	1 6	31	0 2	6 5	+ 129 %	+
ANo	0 8	17	0 1	16 0	0 8	22	0 1	5 5	0 %	0
SL	0 9	16	0 1	15 0	1 8	[illegible]	0 2	6 5	+ 100 %	+
LN	2 0	18	0 3	18 5	2 3	27	0 2	9 5	+ 15 %	0

Table I

Glaucoma simplex

Pat	Before water			IOP	After water			Max change in IOP	Change in F_p	Significance of change in I_p
	I_p	N	S e		I_p	N	S e			
SL	2 5	15	0 2	31 0	3 0	26	0 2	5 0	+ 20 %	0
GN	1 2	15	0 1	22 0	1 3	29	0 1	3 0	+ 8 %	0
AO	0 9	12	0 3	20 0	1 9	22	0 2	1 5	+ 111 %	+
ANo	1 4	20	0 4	23 0	3 3	24	0 5	9 0	+ 135 %	+
IW	1 6	18	0 4	24 0	3 2	27	0.3	8 0	+ 100 %	+
GB	1.3	20	0 2	21 0	1 2	25	0 2	4 0	— 8 %	0
EA	1 2	11	0 1	19 0	1 5	24	0 1	4 0	+ 25 %	0
AJ	1 4	19	0 2	20.5	2 1	28	0 2	—0 5	+ 50 %	+
BJ	1 8	17	0 2	17 0	1 6	26	0 2	4 0	— 11 %	0
ALW	1 8	15	0 2	22 5	1 9	29	0 2	3 5	+ 5 %	0
BJ	2 7	17	0 2	17 0	3 0	28	0 2	3 0	+ 11 %	0
AI	0 5	13	0 1	30 0	0 6	22	0 1	2 0	+ 20 %	0

Table II
Glaucoma Suspects

Pat	Before water			IOP	After water			Max change in IOP	Change in F_p	Significance of change in F_p
	F_p	N	S e		F_p	N	S e			
KO	1 4	16	0 2	18 0	1 7	16	0 2	2 0	+ 21 %	0
ANı	2 2	24	0 1	17 0	3 2	15	0 3	3 0	+ 45 %	+
LH	1 8	12	0 2	21 0	3 1	24	0 2	4 0	+ 72 %	+
HO	[illegible]0	18	0 2	23 0	2 8	24	0 1	11 0	+ 40 %	+
KS	2 3	16	0 2	17 0	3 2	22	0 2	3 0	+ 39 %	+
HO	1 0	16	0 1	22 0	1 4	18	0 1	6 0	+ 40 %	+
UN	1 6	17	0 3	20 5	1 9	27	0 3	4 5	+ 19 %	0
ALW	2 1	19	0 2	19 0	2 7	25	0 2	4 0	+ 20 %	0
BA	1 6	18	0 3	21 0	3 2	[illegible]9	0 4	2 5	+ 100 %	+
UA	0 7	17	0 1	16 0	1 6	31	0 2	6 5	+ 129 %	+
ANo	0 8	17	0 1	16 0	0 8	2[illegible]	0 1	5 5	0 %	0
SL	0 9	16	0 1	15 0	1 8	25	0 2	6 5	+ 100 %	+
LN	2 0	18	0 3	18 5	2 3	27	0[illegible]	9 5	+ 15 %	0

Table III
Normal Patients

Pat	Before water			IOP	After water			Max change in IOP	Change in F_p	Significance of change in F_1
	F_p	N	S e		F_p	N	S e			
CER	1 2	14	0 2	13 0	1 5	19	0 1	1 5	+ 25 %	0
LE	1 6	16	0 4	10 5	3 4	26	0 6	3 0	+ 113 %	+
Sk	0 7	16	0 1	16 5	1 3	20	0 3	5 5	+ 86 %	+
Rk	1 5	16	0 2	17 5	2 1	24	0 1	1 5	+ 40 %	+
MH	1 9	16	0 1	13 0	1 9	26	0 2	4 0	0 %	0
AA	1 6	15	0 2	11 5	2 0	23	0 2	3 0	+ 25 %	0
kMN	1 3	15	0 1	15 5	1 7	25	0 2	0 5	+ 31 %	0
MI k	3 9	16	0 3	16 5	4 6	23	0 4	4 5	+ 18 %	0
RS	0 4	13	0 1	11 5	0 8	26	0 1	1 5	+ 100 %	+

Table IV
No water

Pat	F_p	N	S e	IOI	Γ_p	N	S e	Max change in IOP	Change in F_p	Significance of change in F_p
HK	1 2	16	0 2	20 5	1 4	24	0 1	— 1 0	+ 17 %	0
MA	1 3	16	0 1	21 0	1 5	22	0 1	— 1 0	+ 15 %	0
FT	0 3	15	0 1	17 0	0 5	?3	0 1	+ 0 5	+ 67 %	0
GA	0 4	19	0 1	28 0	0 4	26	0 04	+ 2 0	0 %	0
GA	0 8	14	0 1	19 5	1 4	25	0 2	+ 05	+ 75 %	0)
KK	0 7	14	0 1	18 0	0 5	23	0 1	— 0 5	— 29 %	0
HJ	1 4	14	0 2	20 0	1 9	15	0 2	— 0 5	+ 36 %	0
BJ	1 8	12	0 2	18 5	1 3	2?	0 ?	— 1 0	— 27 %	0

*) signs on the 5 p c level

F_I individual flow mean
N number of separate estimates x_i
S e standard error of the mean
change in F_I on a significance level 97 5 %

Table V

	Time (min)	— 40	— 30	— 20	— 10		+ 15	+ 30	+ 45	+ 60	+ 75	+ 90
Glaucoma spl	F	1 0	1 1	1 1	1 0	water	1 4	1 5	1 3	1 4	1 5	1.5
	s e	0 09	0 08	0 11	0 13		0 20	0 18	0 11	0 20	0 31	0 13
	(n=12)											
Glaucoma susp	F	0 9	0 9	1 1	1 1	water	1 6	1 5	1 3	1 6	1 8*)	1 4**)
	s e	0 06	0 08	0 05	0 11		0 20	0 13	0 09	0 15	0 29	0 25
**) n=6 *) n=10	(n=13)											
Normals	F	0 9	0 8	1 2	1 2	water	1 6	1 6	1 4	1 2	1 6	1 6
	s e	0 11	0 08	0 11	0 09		0 31	0 18	0 16	0 08	0 23	0 24
	(n=9)											
Controls (no water)	F	0 8	1 0	1 2	0 8		1 3	1 1	0 9	1 2	1 2	1 1
	s e	0 13	0 09	0 16	0 09		0 23	0 22	0 10	0 19	0 32	0 11
	(n=8)											

F is a normalized flow value obtained by dividing the actual group mean value by the mean flow before the water ingestion.
s e standard error of the mean

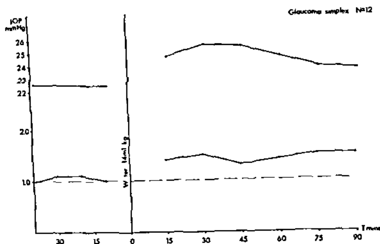


Fig 1
The intraocular pressure (IOP) and relative pupillary flow (normalized to the pre water level) before and after water loading in a group of glaucomas (12 patients)

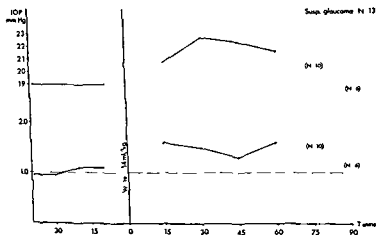


Fig 2
The intraocular pressure (IOP) and relative pupillary flow before and after water loading in a group of glaucoma suspects 13 patients were followed during 60 minutes 10 patients during 75 minutes and 6 patients during 90 minutes

per min it is convenient to normalize each case after its pre water that is all flow values are divided by the mean of the pre water flow level in the same individual

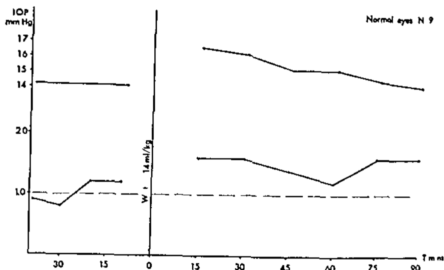


Fig 3

The intraocular pressure (IOP) and relative pupillary flow before and after water loading in a group of normal eyes (9 patients)

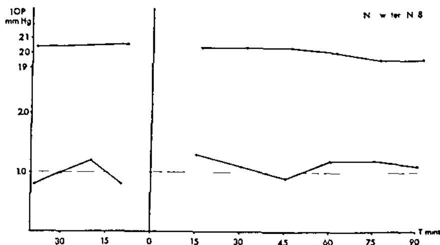


Fig 4

The intraocular pressure (IOP) and relative pupillary flow in a group of glaucoma suspects (8 patients) No water was given

Even at the first observation after 15 minutes the flow is increased by about 50 per cent and it remains increased at the end of the period of observation that is after 90 min when it is still about 50 per cent higher than before water In the control group (Fig 4) in which no water was given there is no significant change of flow The IOP increase soon after the water ingestion is of a magnitude to

be expected from the flow increase if the outflow resistance were kept constant. At the end of the experiment (90 minutes after the water ingestion) the IOP is practically normalized but the flow is still significantly increased. This might suggest a decrease of the outflow resistance at the end of the experiment, i. e. a hint at a pressure regulation. Conclusions of this kind however must be drawn with great caution since we have not proved that the individual curves can be interpreted as samples of a homogenous population.

Summary

In the water provocation test the pupillary flow is increased by about 50 per cent in the mean of the whole material (34 eyes). The flow effect remains for at least 90 minutes when the IOP increase is already normalized.

Acknowledgments

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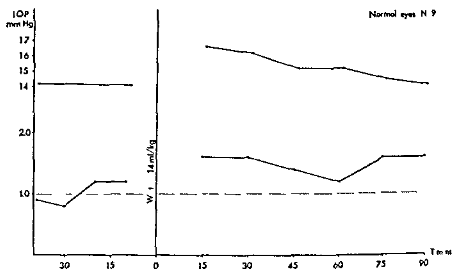


Fig 3

The intraocular pressure (IOP) and relative pupillary flow before and after water loading in a group of normal eyes (9 patients)

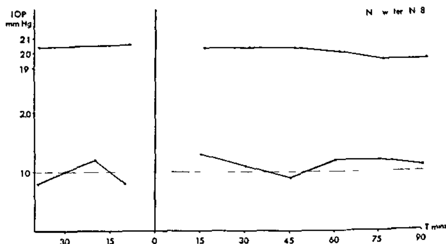


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screen can be supposed to work as shown in Fig 1 The highest intensity is found in the direction of the incident ray and decreasing quantities are emitted with increasing angle of deviation If the source of light is supposed to be an infinitely narrow line of unlimited length (in the x direction) the total quantity of light in a perpendicular strip orthogonal to the light source (the y direction) should be independent of the distance d The shape of the distribution changes with the distance however If the screen distance is increased from d_1 to d the width of the distribution widens by a scale factor $m = \frac{d}{d_1}$ and its height is reduced by $\frac{1}{m}$

Suppose the gradient of intensity which has the direction of the y axis is at a maximum at y_1 when d is d_1 When the screen is moved to d the maximum is at $y = my_1$ The gradient maximum is then $(dI/dy)y_2 = 1/m^2 \ (dI/dy)y_1$ If the source of light emits equal amounts of light in every direction the shape of the distribution depends on the scattering properties of the screen only

The light distribution of the thin horizontal lines which composed all the test objects was recorded by scanning them in the vertical (y)direction (Fig 2) The horizontal slit of a photomultiplier tube was mounted at a distance of about 1 meter from the oscilloscope or the semi translucent screen The test line was imaged by a lens of 50 mm diameter on this slit The test line was slowly moved in the vertical direction making its image pass over the phototube slit The photocurrent was recorded on a storage oscilloscope, the sweep of which was used for driving the test line vertically The position of the test line and the drawing

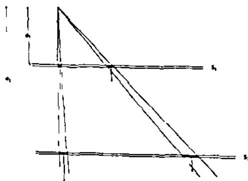


Fig 1
Geometry of light source and the transilluminated plastic screen (s) placed at the distances d_1 and d_2 *in front of the* oscilloscope The light source (L) a line on the oscilloscope extends perpendicularly to the plane of the paper

From the Department of Experimental Ophthalmology
University Eye Clinic Lund Sweden

BLURRED VISUAL STIMULI

I A method for Producing Blurred Stimulus Patterns

BY

C E T KRAKAU & G STIGMAR

The effect of blurring on visual acuity has been tested under various conditions (for ref see *Ogle* 1960 1961) As a rule the blurring has been obtained by de focusation of the retinal image by means of ophthalmic lenses in front of the eye The luminance distribution of the retinal image is then approximately given by the "blur disc" the size of which is found from simple geometrical conside rations Arrangements are necessary for keeping pupillary size and accomoda tion level fixed

The blurring may also be obtained in a more direct way by placing a semi translucent screen in front of the test object This procedure was used by *Harter & White* (1968) in a study of the effect of blurring on visually evoked cortical potentials The present paper deals with this type of blurring which is found to be particularly well suited for the method of testing the visual acuity by test targets on an oscilloscope screen and also for calculations of the light distribu tion of the retinal image

Set up

A light diffusing sheet of a plastic material with a light transmission of about 80 per cent was placed in front of the oscilloscope screen This semi translucent

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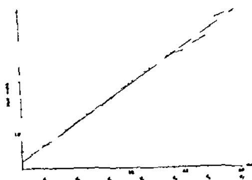


Fig 4
Half width of the distribution (in min arc viewing distance = 3000 mm) versus distance between oscilloscope and the semi translucent screen

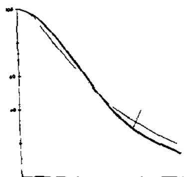


Fig 5
The range of light distributions (d_1–d) normalized to identical height and half width A Gaussion curve (N) is adapted to fall within the limits of the normalized light distributions This normal function satisfies the equation

$$f(x) \quad 11 + 89 \exp - \frac{x^2}{9 \quad 3\,94^2}$$

therefore justified to consider the curves as varying only by scale factors and to use the half width value (w) as a convenient mode of description The blur index introduced by *Fry & Cobb* (for ref see *Fry* 1961) defined as the area of the peak divided by the peak height $I = \frac{A}{h}$ is obviously linearly related to the half width value

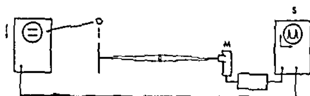


Fig 2
Set up for scanning the light distribution of a luminous object (0) (here two parallel lines) M Photomultiplier S Storage oscilloscope

of its light distribution was thus fully synchronized The luminance distribution of the line as it appeared on the storage oscilloscope was photographed (Fig 3)

The spread of the line image by diffraction is small (about 0 01 mm) in the set up described The photomultiplier slit was 0 035 mm

With increasing distance between oscilloscope and screen the width of the distribution represented by its width at half of the maximum value (half width) increased in a linear fashion (Fig 4) The planimetered areas of the distributions of various widths were similar inside a range of about 4 per cent The shape of the distributions obtained at different distances (d) was compared by normalizing the curves to the same peak and half-width value All curves fell randomly inside the area limited by the two extreme curves indicated in Fig 5

The variation is therefore mainly attributed to random errors in measurement The experiments are thus in agreement with the approximative theory It seems

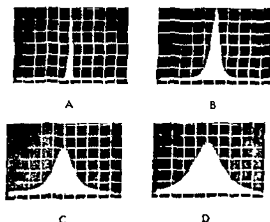


Fig 3
Photographs showing the light distributions of a single line as it appears on the semi translucent screen on different distances (d) Corresponding half widths (w) are A 0 5 B 1 0 C 2 4 D 3 5 mm arc (The amplification has been changed and the total areas are not the same)

the comparator The constant light was measured by means of a calibrated photometer (Hagner mod III) with a spectral sensitivity similar to that of the eye As the relative intensities of the set of test images were measured by means of a photomultiplier tube the luminance of all the objects is calculable from the knowledge of the absolute values for one of them

The luminance of the contour sharp line at its maximum has been estimated at about 100 cd/m² However this value is somewhat uncertain due to the narrowness of the peak of the light distribution. The luminance values for some of the blurred patterns are $d = 38$ $d_4 = 18$ $d_6 = 12$ $d_8 = 6$ All values refer to the maximum of the peak and are expressed in cd/m²

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3 *Harter M R & White C T* Effects of contour sharpness and check size on visually evoked cortical potentials Vision Res *8* 701–711 1968

4 *Ogle K N* Blurring of the retinal image and contrast thresholds in the fovea J Opt Soc Am *50* 307–315 1960

5 *Ogle K N* Foveal contrast thresholds with blurring of the retinal image and increasing size of test stimulus J Opt Soc Am *51* 862–869 1961

The shape of the light distributions has been compared to the normal (Gaussian) density curve It was found that such curves can be fitted inside the extreme curves of Fig 5 provided a constant is added It therefore *seems possible* to take advantage of the analytical simplicity of the Gaussian function in dealing with the present blur effects

The stimulus *patterns in* our experiments are composed of luminous lines of limited length Therefore, when such a line is blurred, the intensity of light emitted from the blurred line will decrease towards its ends The total amount of *light emitted from* the semi translucent screen does not change if the distance (d) between the screen and the oscilloscope is varied but some of the light is scattered outside the ends of the lines The light distribution in the transverse *section at* the end of a long line is easily found if we make use of the fact that another line placed in direct continuation of the first one, restores the intensity to that of an infinitely long line The intensity at the end of the line in the *transverse direction is* therefore half of that obtained centrally provided that the line is long if compared with the dispersion of the blur

The lines in the stimulus patterns used in the investigation have a length of about 4 *min* arc In the central half of the line the intensity difference does not exceed 15 per cent

All the calculations of the light distributions in this investigation are based on values *obtained in* the central part of the lines From the above discussion it follows that the light distribution is flattened towards the ends and this effect will be more pronounced with increasing distance (d) between the semi translucent screen and the oscilloscope

Luminosity of the test image

The test pattern on the oscilloscope screen is generated by the light spot sweeping repeatedly over the screen The image is perceived as a constant light source since the scanning frequency (about 200 Hz) is far above the flicker fusion frequency level According to the Talbot Plateau law flickering light of high frequency is perceived as if it was a constant light of an intensity equal to the mean of the flickering light The mean is defined $L_m = \frac{1}{T}\int_0^T L dt$ This law holds inside a wide range of intensity with great accuracy (for ref see *Brown* 1966) for the eye but not generally for photoelectric devices The mean luminosity has therefore been estimated in the following way The intensity of an oscilloscope line was compared with a constant light source of unsaturated green hue similar to that of the oscilloscope line in a Pulfrich photometer The oscilloscope line had to be diffused by the screen in order to make the surface sufficiently large for

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Table 1

The frequency of fibrillopathy in the general population in earlier materials

Author	Year	No persons	Age	Fibr incid No	Fibr incid per cent	Selection
Rehsteiner	19[illegible]9	238	above 60	4	2	Old people s homes
Hørven E.	193[illegible]	69	50–90	4	6	Old people s homes
Bitran & Villalobos	1959	100	60–99	7	7 0	Old people s home.
Forsius & Eriksson	1961	922	above 40	19	8 5	Population study
Bertelsen et al	1965	618	50– 0	6	1 0	Industrial invest
Ladekarl	1965	250	above 60	5	2	Old people s home
Hollows & Graham	1966	4931	40–75	10	0 2	Population study

The aim of the present study was to investigate the incidence of fribrillopathy in a relatively large population group

Follow up studies of a number of unilateral cases have also been carried out. This study is also intended to serve as a pilot study for the comparison of the occurrence of fibrillopathy in various countries this aspect being discussed in another work by the present author (*Aasved* 1969)

Material

The present material was collected in 1962–63 by mass screening of persons above the age of 40 in 85 industrial concerns and 30 old people s homes in Bergen Norway The examination for fibrillopathy was made with a Haag Streit slit lamp (900) in a darkened room arranged at the factory or institution concerned.

About 90 per cent of the employees/residents presented themselves for examination.

A total of 8 06 persons above the age of 40 was examined.

Of these 169 were disregarded when the material was worked up due to formerly diagnosed unilateral or bilateral eye disease which interfered with the examiner s view of the lens or which might influence the intraocular pressure. In 36 of these glaucoma had been previously diagnosed in 7 cases with fibrillopathy (19 4 *per cent*) *This left* 8 5 31 persons for further analysis 5 688 men (66 6 per cent) and 2 849 women (33 4 *per cent*) *In all* these persons the intraocular pressure was measured and both eyes were examined for fibrillopathy Of the total material 66 residents of old people s homes (10 men and 556 *women*) all above the age of 60 were examined both before and after dilation of the pupils with cyclopentolate hydrochloride (Cyclogyl®)

From the University of Bergen School of Medicine
Department of Ophthalmology
(Head Professor Torstein I Bertelsen M D)

MASS SCREENING FOR FIBRILLOPATHIA EPITHELIOCAPSULARIS,

so-called senile exfoliation or pseudoexfoliation of the anterior lens capsule

BY

HENRY AASVED

The frequency of fibrillopathia epitheliocapsularis (so called senile exfoliation or pseudoexfoliation) has mostly been investigated in materials collected from eye specialist practices at out patient clinics or among patients admitted to eye hospitals (cf Table I *Aasved* 1969) The few materials which are more representative of the general population are shown in Table 1

The table shows a considerable variation in the frequency of fibrillopathy between the materials ranging from 0 2 per cent (*Hollows* & *Graham* 1966) to 8 5 per cent (*Forsius* & *Eriksson* 1961) Most of these materials cover relatively small population groups It is well known that fibrillopathy occurs mainly among persons above the age of 60 and is very rare below the age of 40 However only one of the materials in table 1 shows the occurrence of fibrillopathy in different age groups (*Horven I* 1935) The relation of fibrillopathy to age in the general population is thus a question which has received little attention

Earlier follow up studies of cases with unilateral fibrillopathy show conflicting findings One investigation showed unchanged unilateral occurrence in the course of an observation period of 5 years or more in all 47 patients studied (*Tarkkanen* 1962) *Hansen* & *Sellevold* (1969) found however that fibrillopathy developed in the other eye in 40 8 per cent of the men and 31 0 per cent of the women in the course of a 5 year observation period

Received Dec 6th 1970

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About 80 per cent of the employees residents presented themselves for examination.

A total of 8 [illegible]06 persons above the age of 40 was examined

Of these 169 were disregarded when the material was worked up due to formerly diagnosed unilateral or bilateral eye disease which interfered with the examiner s view of the lens or which might influence the intraocular pressure In 36 of these glaucoma had been previously diagnosed in 7 cases with fibrillopathy (19 4 per cent) This left 8,5[illegible]3 persons for further analysis 5 658 men (66 6 per cent) and 2 849 women (33 4 per cent) In all these persons the intraocular pressure was measured, and both eyes were examined for fibrillopathy Of the total material [illegible]66 residents of old people s homes (10 men and 5[illegible]6 women) all above the age of 60 were examined both before and after dilation of the pupils with cyclopentolate hydrochloride (Cyclogyl®)

Table 2 shows the age distribution of the persons examined The age distribu tion for the two sexes shows good agreement in the groups 50–59 years and 60–69 years There were, however, relatively more men in the group 40–49 years and relatively fewer in the age groups above 70 years The reason for this is that there were more male than female employees at the industrial con cerns but more women than men in the old people s homes

Table 2
Age distribution in mass screening material

Age years	Men no persons	Men per cent	Women no persons	Women per cent	Total no persons	Total per cent
40–49	2303	40 5	788	27 7	3091	36 2
50–59	1908	33 5	919	32 3	2827	33 1
60–69	1203	21 2	626	22 0	1829	21 4
70–79	184	3 2	292	10 2	476	5 6
80–89	86	1 5	206	7 2	292	3 4
90–99	4	0 1	18	0 6	22	0 3
Total	5688	100 0	2849	100 0	8537	100 0

Results

Table 3 shows the occurrence of fibrillopathy in the persons examined

In the whole material fibrillopathy was found in 75 persons 0 9 per cent The youngest person with fibrillopathy was 51 the oldest 90 A clear increase in fibrillopathy was found with increasing age In both sexes combined the in crease was from 0 4 per cent in the age group 50–59 years to 7 6 per cent for persons above the age of 80

In male subjects there was a relatively even increase with increasing age In women there was a marked increase from the age group 60–69 years (1 0 per cent) to the group 70–79 years (6 2 per cent)

Almost the same frequency was found in men and women in the age groups below the age of 70 Above the age of 70 the frequency was higher in women than in men This was also manifest in the total frequency which was 0 5 per cent for men above the age of 40 and 1 7 per cent for women This difference does not appear to have occurred by chance ($P<0\ 01$) Due allowance must however be made for different age distribution in the two sexes A direct

Table 3

Incidence of fibrillopathy in mass screening

Age years	Men			Women			Total		
	no examined	with fibrillopathy	per cent	no examined	with fibrillopathy	per cent	no examined	with fibrillopathy	per cent
40–49	2303	0	0	788	0	0	3091	0	0
50–59	1908	7	0 4	919	3	0 3	2827	10	0 4
60–69	1203	12	1 0	626	6	1 0	1829	18	1 0
70–79	184	5	2 7	292	18	6 2	476	23	4 8
80–89	86	3	3.5	206	20	9 7	292	23	7 9
90–99	4	0	–	18	1	–	22	1	–
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60–69	1203	12	1.0	626	6	1.0	1829	18	1.0
70–79	184	5	2.7	292	18	6.2	476	23	4.8
80–89	86	3	3.5	206	20	9.7	292	23	7.9
90–99	4	0	–	18	1	–	22	1	–
Total	5683	27	0.5	2849	48	1.7	8537	75	0.9

method (*Hill* 1961) was used for this correction with the total material as standard This results in corrected frequencies of 0 6 per cent for men and 1 0 per cent for women

The average age of all the persons examined and of those with fibrillopathy is shown in table 4 The average age of persons with fibrillopathy was higher than that of the whole material in most of the age groups

The distribution of unilateral and bilateral occurrence of fibrillopathy is shown in table 5 In all fibrillopathy occurred bilaterally in 43 per cent some what more frequently among men than among women

The average age of all persons with unilateral fibrillopathy was 71 9 ± 10 1 years with bilateral fibrillopathy 75 0 ± 10 5 years As figure 1 shows most of the persons with unilateral fibrillopathy were in the age group 70–79 years what more frequently among men than among women

Of the 43 persons with unilateral fibrillopathy 10 men and 11 women were reexamined after 6–7 years In 4 men and 5 women fibrillopathy had developed in the other eye (40 and 45 per cent respectively) Twelve of the 21 still showed unilateral fibrillopathy

Comments

Good examination conditions are of prime importance in examinations for fibrillopathy Examinations should be carried out with a slit lamp in a darkened room It must nevertheless be assumed that a certain number of cases of fibrillopathy will escape diagnosis if the examination is carried out without dilatation of the pupils This was demonstrated in the mydriasis material included in the present study Among the 766 persons examined both with undilated pupils and under mydriasis there were 48 with fibrillopathy (*Aasved* 1969) In 5 of these fibrillopathy was not diagnosed until the pupil had been dilated This indicates that approximately 10 per cent of the cases of fibrillopathy escape diagnosis when examinations are made on persons with undilated pupils This was in the higher age groups in which signs of fibrillopathy must be expected to be more marked than in younger persons with a more clearly defined central disk more granulation of the peripheral band and a greater number of flakes on the edge of the pupil In younger age groups a relatively greater number of cases will probably be overlooked on examination without mydriasis It must therefore be assumed that the real incidence of fibrillopathy in persons below the age of 70 is somewhat higher than that found in this study

As expected *an increasing frequency of fibrillopathy was found on increas*

Table 4

Average age for whole material and for persons with fibrillopathy

Age groups years	Men				Women				Total			
	Whole material		With fibrillopathy		Whole material		With fibrillopathy		Whole material		With fibrillopathy	
	Average age	S d	Average age	S d	Average age	S d	Average age	S d	Average age	S d	Average age	S d
40-49	44 5	2 8	–	–	44 8	2 8	–	–	44 6	2 8	–	–
50-59	54 3	2 9	59 9	1 5	54 3	2 9	57 7	1 1	54 3	2 9	54 3	[illegible]
60-69	63 8	2 7	65 0	2 4	63 6	2 9	68 0	1 4	63 7	2 8	66 0	2 6
70-79	73 1	2 9	75 6	2 1	74 2	3 1	76 1	2 4	73 7	3 0	76 0	2 4
80-89	83 4	2 9	84 7	3 5	83 8	2 8	83 6	2 4	83 7	2 8	83 7	2 7
90 99	93 8	3 3	–	–	[illegible]	2 8	90 0	–	97 5	3 0	90 0	–
Total	53 4	9 5	66 0	10 3	58 1	[illegible]	77 3	7 8	55 0	10 7	73 [illegible]	10 3

Table 5
Relative incidence of unilateral and bilateral fibrillopathy

	Men		Women		Total	
	no persons	per cent	no persons	per cent	no persons	per cent
Unilat.	12	44	31	65	43	57
Bilat	15	56	17	35	32	43
Total	27	100	48	100	75	100

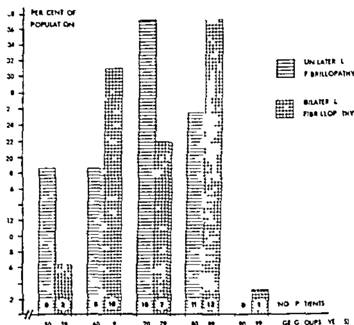


Figure 1
Comparison of the age listribution of 43 persons with unilateral and 32 persons with bilateral fibrillopathy

ing age (table 3) This relation has also been demonstrated in earlier studies of patients both with and without glaucoma (*Lindberg* 1917 *Busacca* 1928 *Horven E* 1935 *Backhaus & Lorentzen* 1966 *Horven I* 1966 *Klouman* 1967 *Sood* 1968 *Larsen*, 1969)

In this study the greatest increase was found in both sexes from the age group 60–69 years to the group 70–79 years This seems to indicate that the incidence of new cases of fibrillopathy is greatest in the age group 70–79 years

Earlier studies of the relation of fibrillopathy to sex have shown conflicting results Some authors have found a higher frequency among women than men (*Horven E* 1935 *Bitran & Villalobos* 1959 *Lowe* 1964 *Backhaus & Lorentzen* 1966 *Klouman* 1967) while others have found the opposite (*Busacca* 1928 *Orgen* 1949 *Joannides et al* 1961 *Gillies* 1962 *Clements* 1968) In the present study some of the difference between men and women may be due to uneven age distribution of the two sexes as the difference was markedly less after correction for age was made. *Nevertheless on the basis of the present study it must be assumed that the incidence of fibrillopathy in the general population is probably somewhat higher among women than among men*

In earlier materials the frequency of bilateral fibrillopathy is given at figures ranging from 33 per cent (*Larsen* 1969) to 84 8 per cent (*Arentsen & Bitran* 1959) The average is probably in the neighbourhood of 50 per cent. In this material the incidence of bilateral fibrillopathy was 43 per cent (table 5)

The average age of persons with unilateral fibrillopathy was lower than that of persons with bilateral incidence for men 6 6 years lower for women 4 7 years lower This difference in average age is a natural consequence of the fact that *unilateral fibrillopathy is often a precursor of bilateral incidence* A total of 43 per cent of the unilateral cases re examined after 6–7 years had thus developed fibrillopathy in the other eye This accords well with the study made by *Hansen & Sellevold* (1969)

In some cases fibrillopathy may be difficult to detect It may therefore be alleged that some cases registered as unilateral are actually bilateral. However in a post mortem material examined histologically 4 out of 6 persons with fibrillopathy were found to be unilateral cases (*Larsen* 1969) There is therefore no doubt that fibrillopathy can occur in only one eye and it is probable that many unilateral cases never develop fibrillopathy in the other eye

Conclusions

Among persons above the age of 40 without eye diseases capable of influencing the intraocular pressure the frequency of fibrillopathy appears to be about 1 per cent The frequency increases with increasing age to 7–8 per cent for persons above the age of 80 The frequency is probably somewhat higher among women than among men. About half of the persons with fibrillopathy are unilateral cases Many of these however develop fibrillopathy in the other eye in the course of a few years.

Summary

Mass screening of 8 537 persons above the age of 40 at 85 industrial concerns and 30 old people s homes in Bergen revealed fibrillopathy in 75 persons i e 0 9 per cent The youngest person with fibrillopathy was 51 years old An increasing frequency was found with increasing age from 0 4 per cent in the group 50–59 years to 7 6 per cent for persons over 80 The observed frequencies are minimum figures as only 766 persons above the age of 60 were examined under mydriasis

Higher frequencies were observed among women than among men 1 7 and 0 5 per cent respectively The difference is partly due to difference in age distribution It is however assumed that the incidence of fibrillopathy is probably somewhat higher among women than among men

In 43 per cent of the cases fibrillopathy was bilateral

A follow up study of 21 of the originally unilateral cases showed that after 6–7 years 9 of these 21 had developed fibrillopathy in the other eye

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Adress of the author

Eye Department Haukeland sykehus
Bergen Norway

From the Coagulation Laboratory (Director Prof I M Nilsson) and from the Eye Clinic (Director Prof G Österlind) Malmo General Hospital University of Lund Malmo Sweden

OUTFLOW RESISTANCE IN THE FOETAL EYE

BY

MAURIZIO PANDOLFI and BIRGER ASTEDT

The development of the aqueous outflow pathways in the human has been the subject of many investigations but nothing is known about the function, if any, of these structures before birth Tonographic values are not available in subjects under 11 years of age (2) Under this age in only one case a premature infant the facility of outflow has been determined by an *in vitro* perfusion method (3) This study deals with the outflow resistance in the eye of human foetuses in various stages of development

Eyes Twenty four eyes were obtained from twelve 17–24 week old foetuses obtained by induced abortion The mothers were healthy and their pregnancies were terminated on socio medical grounds All the foetuses were delivered by abdominal hysterotomy under general anaesthesia with $O_2 + N_2O$ and fluothane The material also included 2 eyes obtained from a premature infant who had died from hyaline membrane disease The crown heel length of each foetus was recorded as was the external diameter of the cornea The eyes were carefully enucleated and immediately processed Also 6 pairs of eyes from adult rabbits weighing 2 0–2 5 kg were examined

Perfusion method The eyes were perfused with sterile unbuffered 0 15 M NaCl by Barány s constant pressure method (1) using a 20 gauge needle at

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tached to a 0 2 ml pipet graduated in 2/1000 ml As a rule the perfusion pres sure was maintained at 27 cm H_2O ($\approx$ 20 mm Hg) When the inflow rate had become steady (generally 5–10 minutes after cannulation) the time required for every 10 μl to enter the eye was recorded and the flow resistance calculated in mm Hg per μl $\times$ min^{-1} To facilitate comparisons with a better known class of values resistance was translated into its reciprocal outflow facility C (μl/min/mm Hg) For conversion to body temperature these values may be multiplied by 1 3 to take into account the decrease in viscosity of saline (3) In view of the deteriorating effect of perfusion fluids on filter resistance (1 5 6) it was thought more appropriate to relate the perfusion to the volume of the liquid perfused rather than to the time elapsed For this reason outflow re sistances were compared at points where equal volumes of perfusion fluid had entered the eye.

Statistical analysis The error of the method was expressed as $\sqrt{\frac{d^2}{2n}}$ $\bar{x}^{-1}$ i e standard deviation of one measurement divided by the mean value of the measurements (4) assuming equal C values for eyes belonging to the same indi vidual Correlations between age body length diameter of cornea (X) on one side and C (Y) on the other were calculated by assuming a linear relationship between X and Y and finding the regression line of Y on X To construct the line the mean C values for pairs of eyes belonging to the same individual were used The correlations between X and Y were read at various significance levels in Student s one tail distribution tables (7)

Results

In 6 human eyes the outflow resistance could not be measured because of diffi culties in the cannulation leakage, or inertia due to the presence of air in the perfusion system. All the eyes successfully perfused showed a comparable pat tern of response Their resistance was greatest shortly after the inflow rate had become steady after which the former successively diminished throughout the perfusion period of up to 4 hours (Fig 1) In view of this washing out effect of saline on the resistance it was decided to consider as representative the resistance value at 0 03 ml i e. when resistance was usually the highest. Table I gives the C values for the human eyes perfused together with age, body length and diameter of the cornea of the foetuses The C values for the rabbit eyes are given in Table II

The calculated error of the method was 18 % for the foetal eyes and 16 % for the rabbit eyes There was a significant increase of the C values with age,

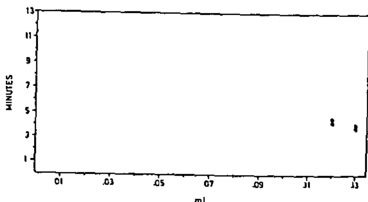


Fig 1

Perfusion of a pair of eyes from an 18 week old foetus Abscissa volume of perfusion fluid entering the eye Ordinate resistance expressed as time in minutes required for 10 μl of saline to enter the eye

body length ($p < 0.05$) and with the diameter of the cornea ($p < 0.01$) Figs 2 3 and 4 show the regression lines for C and age C and body length and C and corneal diameter respectively

In a few cases the perfusion pressure was reduced to 10 mm Hg or increased to 25 mm Hg during perfusion but this change had no noticeable effect on the resistance

Comments

These results show the existence of an efficient system of drainage of aqueous humor in the human foetal eye already in the 17 18th week of age The response of foetal eyes to perfusion fluids with progressively decreasing resistance during the perfusion closely resembles that of adult eyes of primates (6) and of other animals (5) It is however impossible to say whether this foetal drainage system is actually the same as that of adult eyes The error of the method was larger for the humans (18 %) than for the rabbits (16 %) although the number of human eyes was larger The difference was presumably due to the smaller size of the human eyes which were therefore more difficult to can nulate and more liable to be damaged In the small foetal eyes the C values were very small and increased progressively with the development the increase being significantly correlated with age body length and corneal diameter The C value of our premature was comparable to that found by Grant in another premature infant (3) The outflow facility of the rabbit eyes and its variability

Table I

Outflow facilities of 20 eyes from 10 human foetuses and one premature infant together with gestational age body length and corneal diameter Mean C value of each pair of eyes in brackets

	Age of gestation (weeks)	Crown heel length (cm)	Corneal diameter (mm)	Outflow facility (μl/min mmHg^{-1})	
♂	17–18	17	5.5	0 063	
♂	18	25	5 7	0 050 0 049	(0 050)
♂	18	21	5 6	0 042 0 045	(0 044)
♂	19	21	5 8	0 051 0 039	(0 045)
♀	20	22	5 9	0 077	
♂	20	22	5 9	0 032 0 033	(0 032)
♀	20	22	5 7	0 036 0 033	(0 034)
♀	21	20	5 5	0 045 0 048	(0 046)
♂	2[illegible] 23	26	6 7	0 06[illegible] 0 0[illegible]7	(0 0 0)
♂	24	27	6 4	0 047 0 081	(0 064)
♀	29	36	8 4	0 111 0 095	(0 103)

were comparable to that obtained by previous authors with *in vitro* perfusion methods in this animal (8)

Summary

Using *in vitro* perfusion under constant pressure the authors have measured the facility of outflow of aqueous humor of eyes from twelve 17–24 week old

Table II

Outflow facilities of 6 pairs of rabbit eyes.

Rabbit		Outflow facility (μl/min mm Hg^{-1})
1		0 130
		0 150
2		0.376
		0 333
3		0 111
		0 125
4		0 143
		0 250
5		0 233
		0 214
6		0 344
		0 302
	Mean ± SD	0 226 ± 0 094

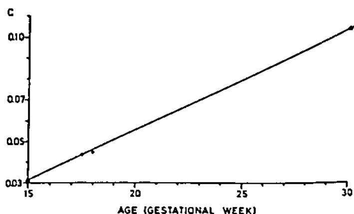


Fig 2

Regression line of outflow facility on gestational age in weeks

human foetuses and from a premature infant The outflow facilities (lowest value 0 032 μl/min/mm Hg in a 20 week old foetus) progressively increased

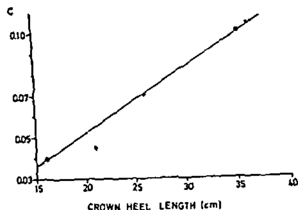


Fig 3
Regression line of outflow facility on crown heel length (cm)

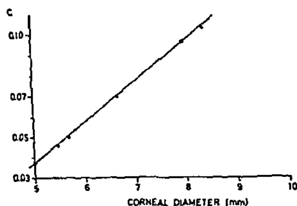


Fig 4
Regression line of outflow facility on cornal diameter (mm)

with the development to reach a value of 0 103 µl/min/mm Hg (mean values of the two eyes) in the premature The increase of C was significantly correlated with gestational age, body length and with the diameter of the cornea.

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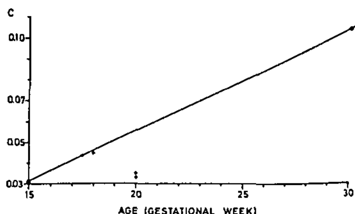


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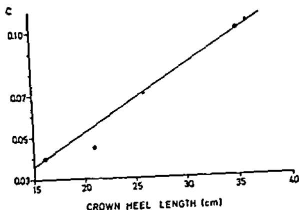


Fig 3
Regression line of outflow facility on crown heel length (cm)

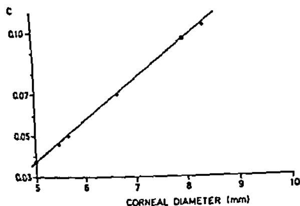


Fig 4
Regression line of outflow facility on cornal diameter (mm)

with the development to reach a value of 0 103 µl/min/mm Hg (mean values of the two eyes) in the premature. The increase of C was significantly correlated with gestational age body length and with the diameter of the cornea.

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5 *Melton C E* & *DeVille W B* Perfusion studies on eyes of four species Amer J Ophthal *50* 302 1960
6 *Pandolfi M* Fibrinolysis and outflow resistance in the eye Amer J Ophthal *64* 1141 1967
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Fonda Gerald Management of the Patient with Subnormal Vision *Second edition.* 167 pages C. V Mosby Co St Louis 1970

The author has many years of experience in the management of subnormal vision and has personally examined more than *4500* partially seeing patients *The fourteen chapters in the book deal with all parts of the subject The first* chapters give a definition of blindness and the incidence and causes of subnormal vision Eye diseases favorable and unfavorable for correction of subnormal vision are listed Braille may be indicated if distance vision is 2/200 or less Visual acuity is more important than blindness alone for learning braille If a patient cannot read *smaller* type than Snellen 2 *M* Jæger 13 or 18 point at a distance 1,5 inches *from the eye it is nescessary* that he learn braille Chapters 3 and 4 deal with the different forms of visual aids for distance and near vision – microlenses magnification, bifocal lenses and telescopic systems Each system is described including the theoretic background and the author gives examples of cases where the patient has *the greatest advantage* of one or the other of *the optic systems Correction with contact lenses nonspectacle magnifiers* and binocular correction are carefully gone over *Only* 20 per cent of 500 patients with vision ranging from 0/ 00- 0/60 experienced binocular single vision. Binocular vision is not frequent when visual acuity is less than 0/200 especially in the presence of nystagmus

Optical aids have limitations The limitations may be connected to the aid or to the *patient Instruction of the patient in the use of a certain optical aid is important* but nevertheless there are groups of patients who never accept an optical aid From the author's experience it seems that more than 30 per cent of patients *more* than 10 years of age use an optical aid successfully when their vision is 20/200 or less

The importance of illumination, theory foveal vision, ophthalmic equipment and the different visual acuity tests *for distance* and *near are described in the following* chapters as well as the procedure for examining patients with subnormal vision *The book is worth reading* and it may be a support for the ophthalmologist *in* the management of the patient with subnormal vision.

Svend Faurschou Jensen

F rlani D Tiberio G & Negroni L. Die Kryotherapie in der Ophthalmologie Bucherei des Augenarztes *Heft 55* Ferdinand Enke Stuttgart 1970 83 pages Price DM. 14 –

In this little easily read book three Italian authors from the University Clinic of Bologna discuss cryotherapy in ophthalmology

The book includes a brief description of 3? different cryo instruments and a detailed description of cryo-cataract extraction and of cryo retino pexy A histologic and ophthalmoscopic description of the course of cryocoagulation is compared with diathermy coagulation and photocoagulation. Other possibilities of cryotherapy (cyclocryothermy in advanced cases of glaucoma simplex cryotherapy *of* small retinoblastoma in the periphery and before intraocular tumour biopsy keratitis) are discussed

The advances and drawbacks of the method are established The indications contraindications and the limitations, compared with other methods are described to the extent made possible by available experience

The book is recommended.

M S Norn

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Aus der Univ Augenklinik Greifswald
(Dir Prof Dr G Gunther)

DIE BIOELEKTRISCHE AKTIVITAT DER NETZHAUT BEI DER DIABETISCHEN RETINOPATHIE

VON

H GLIEM D E MÖLLER & G KIETZMANN

Dem ophthalmoskopischen Befund und seinen modernen Variationen (Biomikroskopie Photographie Fluoreszenzangiographie) kommen bei der Diagnose der diabetischen Retinopathie das uneingeschrankte Primat zu Daneben erscheint uns die Berucksichtigung bioelektrischer Reaktionen aber wichtig da sie von allen funktionellen Untersuchungsmethoden noch am ehesten Ruckschlusse auf den aktuellen Stoffwechselzustand in der Netzhaut erlauben. Die diabetische Mikroangiopathie nimmt ihren Ausgang von den inneren Netzhautschichten, deren quantitativer Anteil an der Potentialbildung hinter dem der ausseren zurucksteht. So aussert sie ihren Einfluss auf das klinische ERG und EOG nur in diskreter in der Literatur unterschiedlich dargestellter Form Es erschien notwendig durch Mitteilung der Ergebnisse einer moglichst grossen Gruppe diabetischer Patienten zur Kenntnis des Problems beizutragen.

Schrifttum

a. Elektrookulogramm

Nach vielen theoretischen und klinischen Erwagungen muss der Ursprungsort des Bestandspotentials in der Hohe der Sinneszellenaussenglieder und des Pig

Re e ved November ?1th 19 0

VARIA

Diabetes und Auge

14 Jahreshauptversammlung der Österreichischen Ophthalmologischen Gesellschaft und Tagung der Vereinigung Bayerischer Augenarzte 10–13 Juni 1971 in Linz Hauptthema Diabetes und Auge"

Teilnahme sowie wissenschaftliche Beitrage an Doz Dr W Funder Kongressekretariat der Wiener Medizinischen Akademie fur arzliche Fortbildung Alserstrasse 4 A 1090 Wien 9 Telephon (0222) 42 71 65 anzumelden

Verteilung (R I) 67 Augen Mikroaneurysmen Sanguinationen harte und Cotton wool Exsudate (R II) 89 Augen proliferative Vorgange aller Stadien (R III) 101 Augen

Methodik

Elektroretinogramm

Gerate EEG (VEB WTGB Berlin) 70 Hz – 0 3 sec Papierdirektschreibung und Oszilloskopfotographie »Duoskop« (VEB Techn Phys Werkstattet Thalheim) Flugelelektrode nach *Henkes* *Reizgebung mit dem* Fotofonostimulator FS 4 FuR Dresden)

Untersuhungsgang Nach 10 min Dunkelanpassung in Mydriasis wurde das ERG mit 8 aufeinanderfolgenden Reizintensitatsstufen (0 2 0 6 2 0 6 0 25 0 50 0 100 0 Ws) ausgelost Ausgewertet wurden die Oszilloskopfotographien Die beiden negativen Komponenten a_1 und a wurden von den isoelektrischen Linie die positiven b_1 und b von der tiefsten Negativitat aus bestimmt Das oszillatorische Potential wurde nach der Anzahl der Gesamtamplitude und dem Quotienten beider Werte bewertet.

Elektrookulogramm

Das Bestandspotential wurde wie ublich auf indirektem Wege durch definierte Augenbewegungen von 30 Grad uber eine bipolare Elektrodenanordnung abgeleitet Die Belichtung erfolgte mit dem Registrieradaptometer des VEB Carl Zeiss Jena Das Bestandspotential wurde zunachst durch eine Praeadaptation von 2 000 lux auf einen Gipfelwert gebracht der als Ausgang und Bezug (= 100 %) diente Der danach folgende Potentialabfall wurde bis zum Talwert im Dunklen verfolgt. Es schloss eine Belichtung bei 2 000 lux an wahrend der die corneoretinale Spannungsdifferenz wieder ihren Gipfelwert erreichte Die beiden letzten Kulminationspunkte werden in Prozent des Ausgangswertes ausgedruckt DA bezeichnet den Talwert der wahrend der Dunkelanpassungsphase erreicht wurde HA den Gipfel *unter der Belichtung Zur naheren Kennzeich*nung wird die Differenz HA – DA verwendet

Statistische Bearbeitung

Zum Vergleich mit den Ergebnissen bei der diabetischen Retinopathie wurden 150 ERG und EOG augengesunder Personen herangezogen Die elektroretinographischen Befunde jedes Retinopathiestadiums wurden sowohl gegenuber der

mentepithels gesucht werden Daher ist die Feststellung von *Francois Verriest & de Rouck* (1957) einleuchtend dass das EOG praktisch nur bei schweren proliferativen Destruktionen der Retina erniedrigt sei Hingegen bemuhten sich *Henkes & Houtsmuller* (1965) u a auch mit Hilfe dieser Untersuchungsmethode den Zustand eines Fundus diabeticus nachzuweisen der einer manifesten diabetischen Retinopathie vorausgehen soll *Kris* (1965) *Kleis* (1967) *Schmidt* (1968) und *Gliem* (1968) stellten bei der retinalen Mikroangiopathie selbst eine Herabsetzung des Belichtungsanstieges fest Wegen der erheblichen Streubreite der elektrookulographischen Untersuchungsergebnisse muss darauf hingewiesen werden dass alle diese Befunde nur an Hand relativ kleiner Patientengruppen gewonnen wurden

b Elektroretinogramm

Fruhere Untersucher (Literaturubersicht bei *Jayle et al* 1965) haben nur in fortgeschrittenen Stadien einer proliferativen Retinopathie subnormale b Wellen ermitteln konnen Nachdem es möglich geworden war die einzelnen Komponenten des ERG gesondert darstellen zu konen fanden *Nagata et al* (1962) den photopischen Anteil bei der diabetischen Retinopathie besonders beeinträchtigt *Sole Alfieri & Lumbroso* (1968) konnten das nicht bestätigen

Besonders Interesse fand das *oszillatorische Potential* des ERG das *Yonemura Aoki & Tsuzuki* (1962) erstmals bei Diabetikern mit einer Retinopathie ausgeloscht fanden Ursprungsort dieser kleinen der b Welle aufgelagerten, aber von ihr vollig verschiedenen »wavelets« ist nach *Yonemura et al* (1963 und 1966) die innere Kornerschicht So erklärt es sich dass *Algvere* (1968) eine Beeintrachtigung bei allen Zirkulationstorungen der Netzhautmitte feststellen konnte Fur die diabetische Retinopathie wurde das von *Kojima et al* (1966) *Tassy* (1966) sowie *Nakajima & Sugimachi* (1968) bestatigt *Simonsen* (1965 und 1968) hatte bei Diabetikern ohne Retinopathie supernormale Werte fur das oszillatorische Potential gefunden

Eigene Untersuchungen

Nach vollstandiger ophthalmologischer und diabetologischer Untersuchung wurde bei 150 zuckerkranken Patienten (insgesamt 291 Augen) des Institutes für Diabetes Karlsburg (Dir Prof Dr H Bibergeil) sowohl das ERG als auch das EOG abgeleitet Das Krankengut teilt sich nach der in Karlsburg gebrächlichen Klassifizierung der diabetischen Retinopathie (R) wie folgt auf Mikroaneurysmen und Sanguinationen in unterschiedlicher Zahl Form und

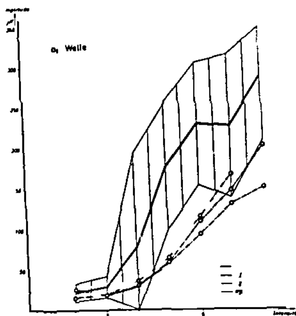


Abb [illegible]

Amplitudenmittelwerte der a_1 Welle (ausgezogene Linie im gestrichelten Feld Normwertmittel oberer und unterer Grenze der Standardabweichung)

setzung der photopischen ERG Anteile wird besonders bei hoheren Reizintensitaten, also einer starkeren Belastung des photopischen Systems deutlich Die Unterschiede zwischen der haemorrhagischen und der exsudativen Form der Retinopathie waren zu gering und konnten statistich nicht gesichert werden Dagegen war die photopische Potentialerniedrigung bei der R III insbesondere bei *hoheren Intensitatsstufen nicht nur gegenuber der Normgruppe sondern* auch gegenuber der R I und R II in hohem Masse statistisch zu beweisen

Vollig verschieden von diesem charakteristischen Verhalten der a_1 und b_1 Welle waren die beiden *skotopischen Wellen* Selbst im fortgeschrittensten Stadium der Erkrankung fiel das Cruppenmittel nicht aus der Streubreite der Vergleichgruppe heraus (Abb 4 und 5) Selbstverstandlich liessen sich auch zwischen den Erkrankungsformen keine Unterschiede finden Die von anderen Autoren als typisch beschriebene Erniedrigung des *oszillatorischen Potentials* konnten wir an unserem Krankengut bestatigen Der Unterschied gegenuber der Normgruppe fiel bei niedrigen Reizintensitaten deutlicher aus als bei hoheren (Abb 6 und 7)

Normgruppe als auch untereinander durch den t Test geprüft Die EOC Werte wurden mit dem Signifikanzschrankentest (*Poser*) bewertet *)

Ergebnisse

Elektroretinogramm

Mit Hilfe der geschilderten Untersuchungsmethodik wurden zwei negative und zwei positive Wellen dargestellt die wir mit *Burian* & *Auerbach* (1955) als a_1 und a_2, b_1 und b_2 bezeichnen Ausserdem trat auf den Photogrammen das oszillatorische Potential deutlich hervor (Abb 1) Die Wellen a_1 und b_1 entsprechen in allen Merkmalen der photopischen a_2 und b_2 dagegen der skotopischen ERG Komponente Bereits die Mittelwertbildung machte das unterschiedliche Verhalten der beiden ERG Anteile deutlich welches durch die statistische Bearbeitung weiterhin zu beweisen war Während sich sowohl die a_2 – als auch die b_2 – Welle nicht von der Normgruppe unterschied befanden sich die beiden photopischen Komponenten a_1 und b_1 bereits im Falle der R I in fast allen Intensitätsstufen an der unteren Grenze der Normbreite Diese Potentialerniedrigung wird bei weiteren Erkrankungsstadien noch deutlicher (Abb 2 und 3) Die Abweichung der *photopischen ERG-Komponenten* von der Norm liess sich mit Hilfe des t-Testes schon für die R I fast ausschliesslich mit einer Irrtumswahrscheinlichkeit von 1–0 1 % sichern Selbstverständlich erhöhte sich die Sicherheit bei den schweren Erkrankungsstadien noch weiter Diese im Gruppenmittel einer grösseren Untersuchungsreihe zum Ausdruck kommende Herab

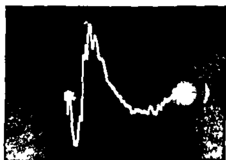


Abb 1

ERG einer augengesunden VP mit ausgeprägtem oszillatorischen Potential

*) Für die Unterstützung bei der rechnerischen Bearbeitung sind wir Herrn Dipl Math *H Poser* Rechenzentrum der E M A Universität Greifswald zu Dank verpflichtet

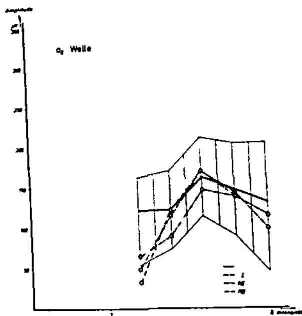


Abb 4
Amplitudenmittelwerte der a Welle

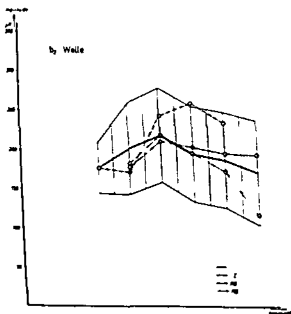


Abb 5
Ampl tudenmittelwerte der b_2-Welle.

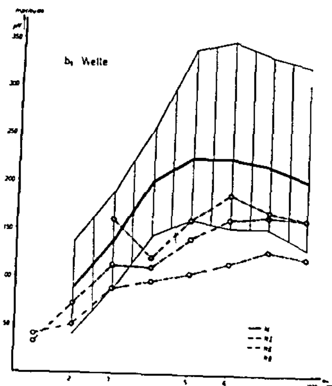


Abb 3
Amplitudenmittelwerte der b_1 Welle.

Elektrookulogramm

Die Beeinträchtigung der Belichtungsreaktionen des Bestandspotentials hat sich wie zu erwarten war als relativ gering erwiesen Tabelle I zeigt die Ergebnisse. Von Interesse ist neben der Einschränkung des Belichtungsanstiegs auch die Erniedrigung des Potentials selbst (Ausgangswert) die mit zunehmendem Erkrankungsgrad festzustellen ist Der Signifikanzschrankentest bewies aber dass nur in fortgeschrittenen Fallen der R III ein sicher positiver Ausfall des EOG zu erwarten ist

Diskussion

Die vorliegende Untersuchung entstand aus dem Bedurfnis auch das ERG und EOG bei der regelmassigen Kontrolle von retinopathiegefahrdeten Diabetikern einsetzen zu können Erkrankungsformen mit malignem Charakter erfordern ein genaues Studium des Verlaufes unter Berücksichtigung aller zur Verfugung stehenden diagnostischen Moglichkeiten insbesondere wenn eingreifende Be

Tabelle 1
Potentialmittelwerte des EOG sowie Mittelwerte des Dunkelabfalls (DA) Hellanstieges (HA) und der Differenz HA DA

Diagnose	Anzahl	Ausgw./µV	DA/%	HA/%	HA DA/%
Norm	*1.0*	*574*	*53*	*119*	*66*
RI	*67*	*531*	*49*	*93*	*56*
		–	–	**	*
RII	89	508	46	116	56
		–	***	–	**
RIII	101	445	52	99	51
		*	–	***	*

Ergebnisse des Signifikanzschrankentestes
– = keine statistische Sicherung
= schwach signifikante stat Sicherung P = 5 %
= signifikante stat Sicherung P = 1 %
= hoch *signifikante stat Sicherung P = 0 1 %*

torischen Potentials um ein diabetes spezifisches und zur Fruhdiagnostik zu verwendendes Zeichen handele erscheint uns nicht *gerechtfertigt*

Interessant sind die Unterschiede zwischen der photopischen und skotopischen Aktivitat im ERG Wenn sie auch nicht erheblich waren und erst im Mittel einer grossen Patientenzahl sowie im Vergleich mit einer ebenso untersuchten Normgruppe zutage traten so durften sie doch fur das Krankheitsbild der diabetischen Retinopathie das den hinteren Funduspol bevorzugt, bezeichnend sein. Fur die Verlaufskontrolle von Diabetikern scheint uns angesichts dieser Beobachtung das *Verhaltnis zwischen skotopischer und photopischer Aktivitat so wie es mit* der Doppelblitzmethode von *Elenius* dargestellt werden kann *von Wert zu* sein Eine kleinere Untersuchungsreihe die wir noch erweitern wollen uber die *in einer spateren* Arbeit berichtet werden soll berechtigt uns zu dieser Auffassung

Die Belichtungsreaktionen des Bestandspotentials und dessen *Amplitude* selbst die wir *Elektrookulogramm* untersuchten lassen sich dagegen nach unseren Erfahrungen kaum zur Fruhdiagnostik und Verlaufskontrolle der diabetischen Retinopathie verwenden Jedoch ist das EOG imstande das elektroretinographische Ergebnis in gewisser Weise zu stutzen Nicht unwichtig ist die Feststellung dass eine bioelektrische Erscheinung wie das Bestandspotential

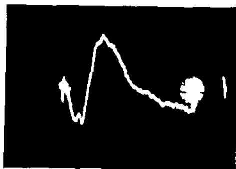


Abb 6

ERG eines Pat mit R III ausgeloschtes oscillatorisches Potential

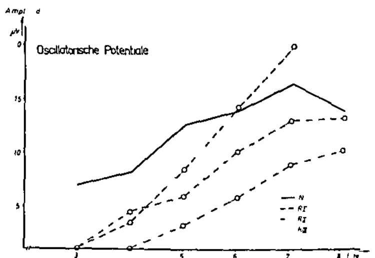


Abb 7

Amplitudenmittelwerte des oszillatorischen Potentials

handlungsmethoden wie die Hypophysektomie oder auch die Photokoagulation in Erwägung gezogen werden

Im *Elektroretinogramm* beobachteten wir wie auch andere Autoren eine deutliche Reduzierung der Anzahl und der Amplituden des oszillatorischen Potentials die dem Erkrankungsgrad entspricht und somit auch zur Verlaufskontrolle des einzelnen Patienten herangezogen werden kann Da diese ERG Komponente nach den gültigen Auffassungen in den inneren Netzhautschichten entstehen soll ist es verständlich dass sie wie bei allen retinalen Zirkulationsstorungen auch auf die Okklusions und Shunt Vorgange der diabetischen Retinopathie empfindlich reagiert Die Meinung dass es sich bei der Ausloschung des oszilla

5 *Gliem H* Die Belichtungsreaktionen des Bestandspotentials Habilitationsschrift Greifswald (1968)
6 *Henkes H E & Houtsmuller A J.* Fundus diabeticus an evaluation of the pre retinopathic stage. Amer J Ophthal *60* 662 (1965)
7 *Jayle G E Boyer R L & Saracco J B* L Electroretinographie Mason et Cie Paris (1965)
8 *Kleiss H* Electrooculographische Untersuchungen bei Retinopathia diabetica Inauguraldissertation, Marburg 1967
9 *Kris E C* Cyclio cornea fundal potential EOG variations etc. ISCERG News letter *6* 88 (1965)
10 *Kojima* The ERG in diabetes Proc. 4th ISCERG J J O Suppl Tokyo *190* (1966)
11 *Nagata M* Clinical evaluation of ERG for its diagnostic value in routine practice in ophthalmology Acta soc. ophth. Jap *66* 1614 (1962)
12 *Nakajima A & Sugimachi Y* Clicinal value of ERG Metabolic disorders Clinical value of Electroretinography S 243 Karger (1968) Basel/New York.
13 *Schmidt B* Persönliche Mitteilung (1968)
14 *Simonsen J E* Electroretinographic study of diabetes Acta ophth (Kb'hvn) *43* 841 (1965)
15 *Simonsen J E* ERG in Diabetes Clinical value of electroretinography S 403 Karger (1968) Basel/New York
16 *Sole P Alfieri R & Lumbroso P* Adapto electroretinography in yellow mono chromatic light in diabetes Advances in electrophysiology and pathology Thieme (1968) Leipzig
17 *Tassy A F* Use of computer technic in clinical ERG Abstr XX Int Congr of Ophthalmology Ghent 1 4th Aug 1966
18 *Yonemura D., Aoki T & Tsuzuki K.* Electroretinogramm in diabetic retinopathy AMA Arch Ophth *68* 19 (1962)
19 *Yonemura D* The oscillatory potential of the electroretinogramm Acta soc. ophth Jap *66* 1566 (196) ref Zbl ophth *88* 197 (1963)

das in den äussersten Netzhautschichten entsteht, bei Patienten mit fortgeschrittenen diabetischen Augenkomplikationen beeinflusst wird

Zusammenfassung

Die Studie ging von der Auffassung aus, dass bei der regelmässigen und umfassenden Kontrolle der Diabetiker nicht auf das ERG und EOG verzichtet werden kann Bei der Untersuchung von 291 Augen mit unterschiedlicher Retinopathie zeigte sich eine vom Erkrankungsgrad abhängige Erniedrigung des oszillatorischen Potentials und der photopischen a und b-Welle im ERG Auffällig war dass auch in fortgeschrittenen Stadien die skotopischen Komponenten des ERG unbeteiligt geblieben waren Mit geeigneter Untersuchungsmethodik kann dieses Verhältnis unmittelbar diagnostischen Wert erlangen Dagegen eignet sich das EOG nur wenig zur Frühdiagnostik und nur bedingt zur Verlaufskontrolle der diabetischen Retinopathie

Summary

The authors prove that the EOG and the ERG are necessary in the course of the continuous and complete control of diabetic patients The examination of 291 eyes in different stages of retinopathy showed a decrease of the oscillatory potential and of the phototopic a and b wave in ERG dependent on its degree The scotopic components in the ERG were not even affected in progressive stages of retinopathy By using an appropriate method this relation will gain directly a diagnostic value Whereas the EOG is of smaller use in the early diagnosis it is only to some extent usable in the follow up of retinopathy

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2 *Algvere P* Studies on the oscillatory potentials of the clinical electroretinogramm Acta ophth (Kbh vn) Suppl *96* (1968)

3 *Francois J* & *Rouck de A* L Electrorétinographie dans la rétinopathie diabetique et dans la retinopathie hypertensive Acta ophth (Kbh vn) *32* 391 (1954)

4 *Francois J Verriest G* & *Rouck de A* L Electrooculographie en tant qu examen fonctionel de la retine. Forschr Augenhk *VII* 1–67 (1957)

Their dependence on the *length* of the visual stimulus has been studied by *French* (1919) *Anderson* & *Weymouth* (1923) *Bair* (1953) and others Thus it have been established that an increasing height of the stimulus lines improves the acuities if the retinal image is restricted to foveola On the other hand vernier and depth discrimination is not influenced by an increase of the *width* of the stimulus lines as shown by *Berry et al* (1950)

The *intensity* of the stimulating light is another factor which influences vernier and stereo acuity For targets of type black on white it has been shown that the acuity improves rapidly in passing from low to moderate levels of stimulation but over a wide range of levels of photopic intensity the acuity is maintained at a high and constant value (*Berry et al* 1948 *Mueller* & *Lloyd* 1948 *Baker* 1949) The same is true also for light bars on a black background as shown by *Leibowitz* (1955) in his study on vernier acuity

The *configuration* of the stimulus pattern affects vernier and stereo acuity in a more complicated way as has been found in several investigations (for ref see *Stigmar* 1970) It has also been suggested (*Stigmar* 1970) that stereoscopic vision if considered from a quantitative point of view can be interpreted as a combination of two monocular vernieroid discriminations if a certain configuration of the test object is chosen For the purpose of this investigation it seems therefore justified to deal with the two kinds of acuity together (the stereo vernier situation)

As regards the *contour sharpness* of the stimulus pattern there is conflicting evidence about its importance for the accuracy of vernier and stereo acuity

The retinal image of a contour sharp stimulus can be characterized by a luminance distribution with a more perfect peaking than that of a stimulus with blurred contours From a more theoretical point of view it might be supposed that a perfect peaking of the retinal luminance distribution would be necessary to achieve the optimal values of vernier and stereo acuity Such a consideration is in line with a theory suggested by *Rohler* (1962)

In an interesting attempt to explain vernier visual function *Rohler* (1962) analysed the contrast transfer function from which the line spread function can be calculated He found that the maximum of the retinal light distribution produced by a single slit formed light source can be localized by a change of 4 per cent in the relative luminance For a single line a decrease of 4 per cent was found to be at a distance of 10 2 sec arc from the maximum of the retinal light distribution, suggesting that this determines the fineness of the vernier acuity

Rohler discusses only the vernier acuity but it is reasonable to presume that the theory should also be applicable to stereoscopic vision since the two kinds of vision are both based on a similar disparity detecting function.

For the stereoscopic visual function, however there are experimental results which indicate that stereoscopic vision is not so much affected as could be expected if the retinal images of both eyes are equally blurred Some of the earlier

From the Department of Experimental Ophthalmology
University Eye Clinic Lund Sweden

BLURRED VISUAL STIMULI

II The Effect of Blurred Visual Stimuli on Vernier and Stereo Acuity

BY

GÖRAN STIGMAR

Introduction

The results of several investigations have shown that the human visual system has the capacity of detecting a vernier off set or a stereoscopic disparity subtending a few seconds of arc That means that the accuracy of vernier and stereo performances is high enough to locate a break in a contour within a small fraction of a cone s diameter since the diameter of the finest foveal cones subtends about 12–20 sec arc (for ref see *Ludvigh* 1953 a)

This well known fact that the dimensions of the receptors in the retinal cone cell mosaic do not limit the capacity of the vernier and stereo acuity was a puzzling mystery for many investigators some decades ago Even with modern knowledge about the integrative processes of the visual system it is difficult to explain how the central visual apparatus can be able to interpret the luminance distribution of the retinal image – more or less degraded by the diffraction and defects of the optical system of the eye – with this degree of precision

One line of attack upon this problem has been to investigate the relative importance for vernier and stereo acuity of the different factors which define the quality of the retinal image By changing the properties of the visual stimulus these various factors can be studied

It is known from earlier investigations that the accuracy of vernier and stereo performances is highly dependent on such factors as the *size intensity configuration* and *contour-sharpness* of the stimulus pattern

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this design has been shown to yield about the same acuity (7–11 sec arc) for vernier and stereo visual functions (for details see *Stigmar* 1970)

The vernier acuity has also been tested with targets with narrower gaps Type A(2) (gaps = 2 min arc) and without gaps Type B (broken line) (Fig 1) With these two targets (extension = 14 min arc) very low thresholds of the vernier function can be obtained (2–4 sec arc)

The luminance of the target was determined as described in part I of this paper In a separate study it was established that the intensity of the stimulus was within that optimal range where vernier and stereo acuity is maintained on a constant level even after some variation of the intensity In fact the intensity of the stimulus could be reduced by about 75 % by filters without any significant decrease of the acuity

The background luminance of the oscilloscope screen was practically zero and the luminous stimulus pattern therefore appeared with optimal contrast.

b) Contour sharpness

Nine different degrees of contour sharpness of the stimulus pattern were used One of them produced without the semi translucent screen was perceived as contour sharp and the others more or less contour degraded by the semi translucent screen were perceived as blurred patterns The targets are designated d_0 d_1 d_8 where d_0 denotes a contour sharp stimulus pattern and d_8 the most blurred pattern To produce the patterns d_1–d_8 the semi translucent screen had to be placed at fixed distances varying from 6 to 110 mm in front of the oscilloscope

It has been shown in part I of this investigation that the light distribution of a luminous line can be characterized in an appropriate way by the half width i e the width of the distribution on half the height of the distribution curve



Fig 1

The three types of stimulus patterns. On the oscilloscope screen they are horizontally orientated The figure illustrates how they are perceived in a vernier situation, when observed through the prismat c device

investigations in this field have been reviewed by *Frey* (1953) and from the results he concluded that a sharp retinal image is not prerequisite for the perception of stereopsis *Ogle* (1962) goes one step further when he states that if the retinal images are blurred – although not too much – "this may result in only a small decrease in stereoscopic acuity from that with a sharp imagery

There are no recorded experimental studies on vernier acuity like those referred to on stereoscopic acuity apart from a notice in a paper by *Hartridge* (1923) Working with a test object consisting of absorption bands he observed that objects with blurred outlines can also under certain circumstances be set into alignment with approximately the same accuracy as contour sharp lines

Most experiments with blurred retinal images concern the resolving power of the eye It can be predicted merely for physical reasons that the resolving power of the eye, contrary to the vernier or stereo acuity will be deteriorated by blurring the stimulus pattern The present investigation however has been restricted to the vernier and stereo acuities

Methods and Materials

The technique of characterizing and producing stimulus patterns with various amounts of blur described in part I of this paper has been used in this study for an investigation of the influence of contour degradation on vernier and stereo acuity

General feature of the experiments

In previous investigations (*Krakau* 1967 *Stigmar* 1970) it has been shown that stimulus patterns produced on an oscilloscope screen can be used as targets for the examination of vernier and stereo acuities The target is observed through two Dove prisms Depending on the position of the prisms either a vernier or a stereo situation can be achieved

The target

a) Shape and luminance

Three types of target A(7) A(2) and B have been used (Fig 1) The target of Type A(7) consists of three lines of equal length each subtending an angle = 3 3 min arc two reference lines at each end and a middle line vertically displaced with a certain variable distance (the vernier off set) The three test details of the target are separated by gaps subtending an angle = 7 min arc giving a total extension of the target = 24 min arc For most observers a target of

A(?) and B respectively but the other arrangements were the same as in series A_1

The subjects

The subjects taking part in the study were all familiar with the examination procedure Their binocular visual functions were normal and they had a corrected visual acuity of $\geq 1\ 0$ (Monoyer s letter chart)

Six subjects took part in the first part of the examination (Series A_1) Three of them were re examined with the same experimental procedure apart from the mode of blurring the target (Series A_2) and – during other sessions – with the optimal vernier targets (Series A(2) and B)

The recording procedure Definitions

The subjects were presented with an alternative situation right or left, in front of or behind for the vernier and the stereo situation respectively The magnitude of the vernier off set or stereo disparity was automatically adjusted in a step like way by the interpretations of the subject. The magnitude ratio of two consecutive steps was always 1 2

For each type of target and for each modification of the contour sharpness the visual performances were recorded over a 5 minute period The recordings during the last four minutes of examination have been the basis for the calculation of the thresholds

The arithmetic mean (M) and the standard deviation (s d) of the dispersion of transitions from one step to the next one during this period have been chosen as suitable variables for the characterization of the curve In previous papers (*Krakau* 1967 *Stigmar* 1970) the statistical properties of the value of M have been described and analogously in this paper also M has been used to describe the disparity discriminative capacity of the subject and is denoted the threshold value

At threshold the vernier off set (a_{vt}) subtends a visual angle $(\nu_t) = \frac{a_{vt}}{D}$

and the stereo disparity ($2a_{st}$) subtends an angle $(\eta_t) = \frac{2a_{st}}{D}$

if D = the observation distance and a_t = the linear distance of displacement at threshold on the oscilloscope screen

Results

a) Series A_1

Vernier and stereo acuity was determined for a target of Type A(?) It was

The half-width of the light distributions for the different degrees of blur had the following values $w_0 = 0.5$, $w_1 = 0.7$, $w_2 = 1.3$, $w_3 = 1.9$ $w_4 = 2.5$ $w_5 = 3.1$, $w_6 = 3.7$, $w_7 = 4.4$ $w_8 = 7.6$ min arc

Since the targets A(7) A(2) and B consist of pieces of luminous lines with a defined light distribution, the contour-sharpness of the patterns as an entirety is also defined by the value w By using targets with different separation distances (7 2 and 0) between the edges of the test details the importance of distinctly perceived edges for the achievement of very low thresholds can be studied

The binocular visual field of the observer was restricted by screens with a central aperture to an area that subtended a visual angle of about 10° The screens were slightly illuminated (2 cd/m) and the contours of the apertures of the screens served as a stimulus for the convergence and the accomodation The experiment was otherwise conducted in a darkened room Examination distance was 3000 mm (For details see *Stigmar* 1970)

Types of experiments

Four series of experiments were performed A_1 A_2 A(2) and B In series A_1 a masking was placed closely in front of the oscilloscope thereby blurring the test details in all directions of the vertical plane thus also in the spaces between the test details In series A_2 the masking was placed just behind the semi translucent screen limiting the blurring to an area perpendicular to the extension of the luminous lines but with the gaps between the test details free from blurring (Fig 2) A stereo vernier target of Type A(7) was used as test object in these two series In the series A(2) and B the vernier acuity was tested with the targets Type

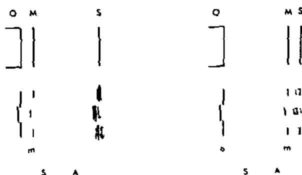


Fig 2

The different types of stimulus patterns are produced by masking (M) the oscilloscope line (o) A blurred pattern (s) is produced by the semi translucent screen (S) and by changing the distance O–S the degree of blur can be varied If the mask (M) is placed just behind the screen (S) as in Series A_2 the gaps become free from blur

Table I

Vernier and stereo thresholds of 6 subjects for a target Type A(7) with different degrees of contour sharpness (Series A_1)

	d_0 w=0.5		d_1 w=0 7		d w=1.3		d_3 w=1 9		d_4 w=[illegible].5		d_5 w=3 1		d_6 w=3 7		d_7 w=4 4		d_8 w=7 6	
	ζ_t	η_t	ζ_t	η_t	ζ_t	η_t	ζ_t	η_t	ζ_t	η_t	ζ_t	η_t	ζ_t	η_t	ζ_t	η_t	ζ_t	η_t
Subject																		
CS	14 3	15 0	10 8	11 2	9 8	12 6	13 2	17 [illegible]	10 3	13 [illegible]	9 8	14 8	7 1	15 [illegible]	11 0	13 6	12 4	29 0
VW	6 7	6 3	6 6	5 0	6 8	4 9	9 8	4 9	12 6	[illegible] 9	11 0	10 0	10 8	4 7	7 0	6 2	9 2	13 0
LC	7 4	8 1	8 3	7 5	9 2	9 4	7 [illegible]	6 7	5 6	9 4	6 1	6 5	7 2	6 3	4 [illegible]	7 2	9 8	14 3
IB	13 8	9 2	16 3	8 4	12 2	5 [illegible]	18 7	10 8	11 [illegible]	6 [illegible]	14 0	6 5	10 3	7 4	15 0	7 7	18 1	14 5
RU	5 9	5 6	10 [illegible]	7 0	6 3	6 2	5 4	9 6	7 [illegible]	6 3	6 1	4 [illegible]	8 9	6 1	10 0	6 5	14 5	11 0
US	13 0	10 3	1[illegible] 6	4 9	9 0	7 [illegible]	[illegible] 3	5 8	9 8	6 6	9 0	7 5	8 9	6 3	12 8	5 9	16 3	15 0
M	10 2	9 1	10 8	7 3	8 9	7 6	10 4	[illegible] 2	[illegible] 6	7 9	9 3	8 3	8 9	7 7	10 0	7 9	13 4	16 1
(n=6)																		
s d	3 9	3 4	3 4	2 3	[illegible] 1	2 9	4 8	4 5	[illegible] 5	2 9	3 0	3 7	1 5	3 9	3 9	2 9	3 6	6 5
M (vernier) minus M (stereo)	1 1		3 5		1 3		1 3		1 7		1 0		1 2		2 1		-[illegible] 7	
s d	1 7		3 4		[illegible] 5		2 5		1 8		2 8		[illegible] 8		2 6		5 5	

The vernier (ζ_t) and stereo (η_t) thresholds are expressed in sec arc w = half width of a single line of the target

presented for the 6 subjects as a contour sharp pattern (d_0) and with different degrees of contour degradation (d_{1-8}) The individual results expressed in seconds of arc, are shown in Table I The averaged values (M) for vernier and stereo acuity respectively, are graphically illustrated in Fig 3

The graph shows that the acuities are maintained at a stable level with increasing contour degradation of the pattern from d_0 to d_4 which corresponds to an increase of the half value width (w) from 0 5 to 4 7 *minutes of arc. In the* range d_1 d stereo thresholds are somewhat lower than those of vernier not *significantly* however, as shown in Table I

b) Series A

In this series the extension of the irradiation of light has been limited by a type of *masking so that the* gaps between the test details become free from blur 3 subjects from Series A_1 were re examined with this method and their averaged performances in the two series respectively can be compared in a graph (Fig 4)

The individual results in Series A are also shown *in Table II* The conclusion which can be drawn from the comparison between the Series A_1 and A will be that the irradiated light in the gaps (series A_1) makes the alignment procedure for the most contour degraded patterns (d d_8) *somewhat easier*

c) Series A(2) and B

The individual results obtained by blurring *the targets* A(2) *and* B are presented in Tables III and IV respectively In the graphs (Figs 5 and 6) the averaged performances (M) and the dispersion of the individual results are also indicated The results in these series show that blurring *affects the vernier* thresholds obtained with the stimulus pattern of types A(2) and B relatively more than those obtained with type A(7)

Discussion

a) The stereo vernier relationship with blurred targets (Series A_1 and A)

In the series A_1 and A a stimulus pattern of type A(7) *has been* utilized for an evaluation of the effect of blur on vernier and stereo acuity From the Tables I–II and Figs 3–4 it can be seen that there is no significant difference between vernier and stereo performances if the test details of the blurred pattern have a half-width w = 1 4 More extensive blurring (w = 7 6) seems to affect the stereo acuity more than the vernier acuity

The close relation between vernier and stereo acuity which can be established for the contour degraded patterns d_1 d in both the series A_1 and A_2 is in line

Table II

Vern er an l stereo thresholds for different degrees of contour sharpness of *the target* Type A(7) where the gaps between the test details are free from blur (Series A)

	d_0		d_1		d_3		d_5		d_7		d_8	
	ζ_t	η_t	ζ_t	η_t	ζ_t	η_t	ζ_t	η_t	ζ_t	η_t	ζ_t	η_t
S bject												
G S	14 3	15 5	13 0	9 0	11 0	16.3	13 0	10 5	10 0	20 8	34 0	75 8
V W	6 7	6 3	9 4	5 0	10 5	5 9	9 8	7 9	10 0	12 8	13 0	29.5
I G	7 4	8 1	4 8	7 1	5 2	5 1	10 1	6 5	11 6	5 8	13 2	25 0
M (n = 3)	9 5	9 8	9 1	7 0	8 9	9 1	11 0	8 3	10 5	13 0	20 1	43 4
M (vernier) minus M (stereo)	-0 3		2 0		-0 2		2 7		-2 4		-23 4	

The symbols used are the same as those in Table I Thresholds in sec arc

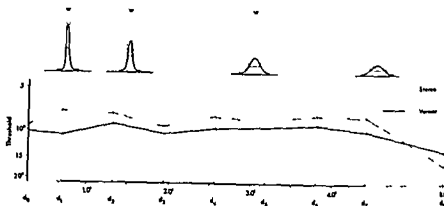


Fig 3

Vernier and stereo thresholds (in sec arc) obtained with increasing contour degradation (blur) of the stimulus pattern Type A(7) The half width of the light distribution of a single line is plotted on the abscissa It should be pointed out that identical threshold values for vernier and stereo functions ($\zeta_t = \eta_t$) means that the corresponding vernier off set (on the oscilloscope) is in the stereo situation half of that in the vernier situation

with the results of an earlier investigation (Stigmar 1970) indicating that vernier and stereo visual functions are based on a similar disparity detecting mechanism provided that the stimulus pattern has a certain design (like that of Type A(7)) This conclusion can therefore be extended to be valid not only for contour sharp targets but also for blurred ones where the contour sharpness has been considerably changed

b) The vernier acuity with different types of targets

As was predicted the lowest vernier thresholds are obtained with a contour sharp target of type broken line (Type B) and the more the test details are separated (Type A(2) and A(7)) the higher thresholds are obtained This relation between the vernier performances with different types of targets is maintained even when the stimulus pattern is slightly blurred (Figs 3 5 and 6) but an increasing amount of blur influences the results obtained with the three types of targets differently With a stimulus pattern of Type A(7) the half width of a single line can be increased about 9 times ($w_0 = 0.5$ $w_7 = 4.4$) without any change in the vernier acuity The corresponding value obtained with target Type A(2) is about 7 times ($w_6 = 3.7$) and that obtained with target Type B is about 3 times ($w = 1.3$) It is evident that an optimal vernier acuity can be obtained only if there is a distinct edge between the displaced vernier off set and the reference lines However if the test details are spaced the vernier thresholds are remarkably unaffected by a change in the light distribution of the pattern

Table III

\ern er thresholds for different degrees of contour sharpness of the target Type A(°)

	d_0	d_1	d	d_3	d_4	d_5	d_6	d_7	d_8
	ζ_t	ζ_t	ζ_t	ζ_t	ζ_t	ζ_t	ζ_t	ζ_t	ζ_t
Subject									
G S	4 7	4 1	5 7	7 0	6 2	6 6	7 2	9 0	32 5
V W	4 2	5 2	5 6	3 9	5 3	5 8	6 2	7 6	15 8
I G	3 7	3 [illegible]	4 9	3 5	4 [illegible]	5 2	3 7	7.3	27 0
M (n = 3)	4 2	4 2	5 4	4 8	5 2	5 9	5 7	8 0	25 1

The symbols used are the *same* as those in Table I *Thresholds in sec arc*

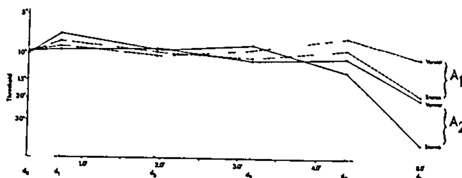


Fig 4
Vernier and stereo thresholds as a function of increasing blur for target Type A(a). Averaged values for 3 observers obtained in Series A_1 (dotted lines) and Series A (continuous lines)

c) The effect of blurred stimuli upon the retinal image

Our series of blurred stimulus patterns (d_0 d_5) represent light distributions the half widths of which cover the range from 0 5 (w_0) to 7 6 (w_5) min arc The ratio between the two half widths i e between the most and the least blurred line will thus be about 15

This quotient however does not adequately describe the change between the light distributions of the corresponding retinal images

An infinitely thin line is imaged on the retina as a distribution of finite width This line spread function "is a direct measure of the imaging quality of the eye and "mathematical manipulation of this spread function allows definition of the quality and properties of the image of any light distribution given in space (cit *Fankhauser* & *Rohler* 1967)

The line spread function of the individual eyes of the subjects taking part in this investigation has not been determined but from the investigations by *Flammant* (1955) *Rohler* (1962) *Westheimer* & *Campbell* (1962) and *Campbell* & *Gubisch* (1966) it is possible to make a crude estimate of the half width of the spread function For a pupillary size = 3 mm it is found to have a magnitude of about 1 5 min arc

As has been shown in part I of this paper the blurred lines have light distributions which are approximately of a Gaussian shape If we suppose that the line spread function also has a Gaussian shape we can make use of the fact that convolution of two normal density functions with the dispersion s_1 and s_2 is a new normal function with the dispersion $s = \sqrt{s_1^2 + s_2^2}$ Therefore applying such a rough calculation on our series we can obtain an estimate of the half widths of the images of the different stimulus patterns With this approach the half width of the retinal light distribution of an unblurred line can be estimated

Table III

Vernier thresh lds for different degrees of contour sharpness of the target Type A(2')

	d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	d_8
	ζ_t	ζ_t	ζ_t	ζ_t	ζ_t	ζ_t	ζ_t	ζ_t	ζ_t
Subject									
G S	4 7	4 1	5 7	7 0	6 [illegible]	6 6	7 2	9 0	32 5
V W	4 [illegible]	5 2	5 6	3 9	5 3	5 8	6 2	7 6	15 8
L.G	3 7	3 [illegible]	4 9	3 5	4 2	5 2	3 7	7 3	27 0
M (n = 3)	4 [illegible]	4 [illegible]	5 4	4 8	5 2	5 9	5 7	8 0	25 1

The symbols used are the same as those in Table I *Thresholds in sec arc*

Table IV

Vernier thresholds for different degrees of contour sharpness of the target Type B

	d_0	d_1	d_2	d_3	d_4	d_5	d_6	d_7	d_8
	ζ_t	ζ_t	ζ_t	ζ_t	ζ_t	ζ_t	ζ_t	ζ_t	ζ_t
Subject									
G S	3 6	3 1	4 1	4 4	9 4	10 7	10 6	13 0	32 5
V W	2 5	2 4	2 2	3 4	3 6	3 4	3 7	5 8	15 8
L G	2 6	3 7	3 3	3 8	4 4	5 7	6 3	6 2	27 0
M (n = 3)	2 9	3 1	3 2	3 9	5 8	6 6	6 9	8 3	25 1

The symbols used are the same as those in Table I Thresholds in sec arc

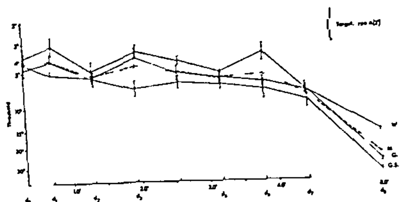


Fig 5
Vernier thresholds as a function of increasing blur for target, Type A(2') for 3 observers M = averaged performances

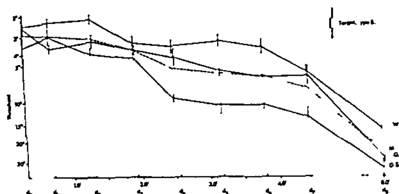


Fig 6
Vernier thresholds as a function of increasing blur for target Type B for 3 observers M = averaged performances.

to 1 6 and the most blurred to 7 8 The ratio between these values is about 5 and can be taken as an approximative value, indicating the effect of the induced blurring (w_a w) of the retinal images

The fact remains that the retinal image can be blurred to a considerable degree without any perceivable reduction in vernier and stereo acuity Thus with a stimulus pattern of Type A(') the acuity is still maintained on the 10 second level even if the half widths of the stimulus lines are increased 9 times which corresponds to an increase of the retinal image of about 3 times and a decrease of the gradient of about 8 times.

The contour sharpening mechanisms of the visual system such as Mach's band are a function of the gradient slope of the luminance distribution curve as shown by *Mach* (1868–1906) and *Ludvigh* (1953 b) Then it follows that these mechanisms must be less pronounced the more the luminance is smoothed out in the retinal image, a fact which excludes Mach's band and allied phenomena as responsible for the stable performances even with quite a blurred stimulus

Our results are in accordance with the experimental results mentioned by *Frey Ogle and Hartridge* but hard to combine with *Rohler's* theory The results are somewhat surprising, since it seems intuitively natural to look at the retinal light distribution as related to a statistical distribution the mean of which is better defined the smaller the dispersion On the other hand, if a sharp retinal image" is blurred a greater number of light receptors will be stimulated and involved in the determination of the peak of the light distribution

Summary

Earlier investigations have provided conflicting evidence as regards the relative importance of a sharp imagery for the achievement of the high accuracy of vernier and stereo performances To investigate that problem the effect of blurred visual stimuli on the two visual functions has been studied

Luminous stimulus patterns with different degrees of contour sharpness (blur) were produced by a diffusing semi translucent screen The luminance distribution of the patterns was determined by using the technique described in part I

If the stimulus pattern consists of test details separated by a distance = 7 min are the vernier and stereo acuity are maintained at a high and constant level even with considerably blurred targets With decreasing distances between the test details the vernier acuity deteriorates at lower degrees of blurring

The changes in the luminance distribution of the retinal image induced by contour degradation of the stimulus pattern have been estimated The results indicate that a high level of acuity can be maintained in spite of an increase of the blur = 9 times the width of the stimulus lines corresponding to an increase = 3 times the retinal images if measured in terms of half widths of the light distribution curves

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mal eyes except for refractive errors less than 3 D and presbyopia Each group consisted of 15 subjects 12 females and 3 males 5 individuals with wn iris and 10 with blue (or grey) iris were selected in each age group
oth drugs were given to each test subject randomly in the right and the left
We used subjects with no measurable difference in the size of their two ils and obtained by this arrangement the advantage of having the same ing sizes of the pupils in the cyclopentolate and the phenylephrine group
No other eye drops were used and tonometry was not performed before the t was completed thereby eliminating a possible influence on the resorbtion the drugs by damage to the corneal epithelium
The pupils were measured under standard artificial light conditions in a rk room with full face illumination from a single lamp with a 60 Watt 220 lt bulb in a white reflector of 16 cm diameter (Luxo lamp) The lamp was iced at a distance of 2 5 m and about 15° above the horizontal plane The bjects were looking at the light when the pupils were measured thereby ob ining a standard direction of gaze in relation to the light and also a constric on of the pupil similar to the one evoked by the light of an ophthalmoscope
The horizontal diameter of the pupil was measured with the help of a caliper he measurement was performed in two steps first the caliper was adapted to e apparent size of the pupil thereafter the distance between the two pointed gs was determined by the help of a scale attached to the caliper The move ents of the pointer on the scale were magnified about 1 5 times as compared ith the relative movements of the legs By this arrangement the measurements ere found to be sufficient accurate to permit the results to be set down to the earest 1/10 mm although for the single measurements the last cipher can not e considered exact
After an adaption period of 5 minutes the first measurement was performed nd the result was recorded as the resting size of the pupil. Two drops of the nydriatic were instilled in each eye Thereafter the measurement was repeated every 5 minutes in the first 1/2 hour and every 10 minutes in the following hour

Results and discussion

The results of the measurements are illustrated in the figures 1 2 and 3 which show the average values and the standard deviations
It is seen that cyclopentolate dilates the pupil much quicker than phenyl ephrine both in the young and in the old group The average time to reach maximal mydriasis is ca. 25 min. after cyclopentolate and ca. 6 min. after phenylephrine both in the young and in the old group (table 1) The average of the maximal size of the pupils in the different groups is also seen in table 1

From the University of Oslo Department of Ophthalmology
(Head Professor dr med Thore Lie Thomassen)

MYDRIATICS AND AGE

BY

ANDERS BORTHNE and MARTIN DAVANGER

Slit lamp examination of iris reveals that senile changes are common in this structure. The iris stroma is often atrophic in old people and the iris vessels may be sclerotic. The reduction of the size of the pupil with increasing age hangs probably together with these morphological changes of iris.

While the senile miosis is well known, a possible influence of age on the effect of mydriatics does not seem to be reported. A comparison of mydriasis obtained with different mydriatics in young and in old people may be of interest, both from a practical point of view and because this comparison may elucidate age changes of iris from a physiological point of view.

Material and methods

Two different commonly used mydriatics have been used in this trial, namely cyclopentolat hydrochloride (Cyclogyl®) 1 % and phenylephrine (Metaoxedrin) 10 %. Both drugs were used in the usual composition as eye drops as supplied by the pharmacy. pH was measured to be 4.8 in Cyclogyl® and 3.3 in the phenylephrine drops.

The effect of the two mydriatics was studied in two different age groups: a young group of 19–25 years and an old group of 60–75 years, average age 21.8 and 66.0 years respectively. The young subjects were nurses and students, in the old group were patients consulting our out-patient clinic. All individuals had

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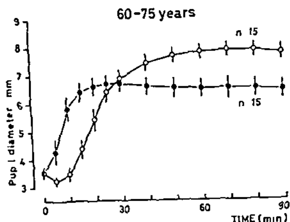


Fig 3
The mydriatic effect in old individuals
● Cyclopentolate. o Phenylephrine.
The vertical lines indicate 1 standard deviation.

Table 1
Maximum size of pupil Time taken to reach the maximum size In each class the average of 15 individual values is given

Mydriatic	19-25 years	60-75 years
Cyclopentolate 1%•	8 0 mm St. dev 0.37 mm 9 min.	6 7 mm St. dev 0 61 mm 24 min
Phenylephrine 10%	6 8 mm St. dev 0 83 mm 67 min.	7 8 mm St. dev 0 49 mm 68 min.

In the figures 2 and 3 the standard deviations are given It is seen that when full mydriasis has been reached, the scatter of the individual values tend to be smaller in the group with the highest average value. The reason may be that mydriasis in these cases is approaching the maximum obtainable.

The well known reduction of the size of the pupil with age is seen also in this

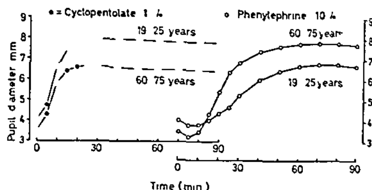


Fig 1
The mydriatic effect of Cyclopentolate 1 % and Phenylephrine 10 %

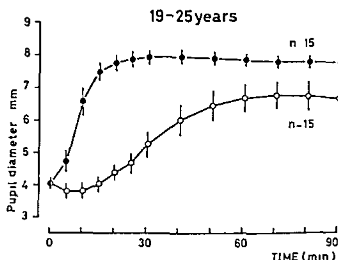


Fig 2
The mydriatic effect in young individuals
● Cyclopentolate o Phenylephrine
The vertical lines indicate 1 standard deviation

There is a marked discrepancy between the young and the old group regarding the effect of the two different mydriatics used In young individuals cyclopentolate gives better mydriasis than phenylephrine while the opposite is true in the old individuals The difference between the averages of the maximal mydriasis in the young and the old group after cyclopentolate and after phenylephrine is highly significant The difference between mydriasis obtained with the two different mydriatics in the young and in the old group is also highly significant (table 2)

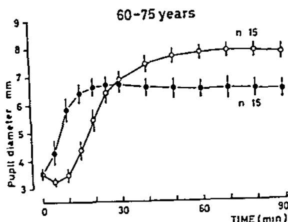


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Maximum size of pupil Time taken to reach the maximum size In each class the average of 15 individual values is given.

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Cyclopentolate 1%	8.0 mm St dev 0.37 mm 27 min	6.7 mm St. dev 0.61 mm 24 min
Phenylephrine 10%	6.8 mm St dev 0.83 mm 67 min.	7.8 mm St. dev 0.49 mm 68 min

In the figures 2 and 3 the standard deviations are given. It is seen that when full mydriasis has been reached the scatter of the individual values tend to be smaller in the group with the highest average value. The reason may be that mydriasis in these cases is approaching the maximum obtainable

The well known reduction of the size of the pupil with age is seen also in this

Table 2

Differences in average size of pupil. Calculations of significanse.
(Student's t test)

time = 0 minutes		
Young – old	4.06 – 3.50 = 0.56	P<0.001
Blue iris – brown iris, total	3.89 – 3.56 = 0.33	0.025<P<0.05
Blue iris – brown iris young group	4.19 – 3.80 = 0.39	0.0[illegible] <P<0.05
Blue iris – brown iris old group	3.59 – 3.32 = 0.27	0.05 <P<0.10
Maximum size of pupil		
Cyclopentolate young – old	7.97 – 6.67 = 1.30	P<0.001
Phenylephrine, old – young	7.83 – 6.79 = 1.04	P<0.001
Young group cyclopentolate – phenylephrine	7.97 – 6.79 = 1.18	P<0.001
Old group phenylephrine – cyclopentolate	7.83 – 6.67 = 1.16	P<0.001
Young cyclopentolate blue – brown	8.16 – 7.58 = 0.58	0.001<P<0.005
Young phenylephrine blue – brown	7.14 – 6.08 = 1.06	0.005<P<0.01
Old cyclopentolate blue – brown	6.90 – 6.22 = 0.68	0.02 <P<0.05
Old phenylephrine blue – brown	7.99 – 7.52 = 0.47	0.05 <P<0.10
Difference between maximal and resting size.		
Young cyclopentolate	7.97 – 4.06 = 3.91	
Young phenylephrine	6.79 – 4.06 = 2.73	
Old cyclopentolate	6.67 – 3.50 = 3.17	
Old phenylephrine	7.83 – 3.50 = 4.33	

material in which the average size of the pupil in the untreated eye is 4.06 mm in the young and 3.50 mm in the old individuals. The difference is highly significant (table 2).

The resting pupil is found to be on an average slightly smaller in eyes with brown iris than in eyes with blue iris. This was also found by *Obianwu* & *Rand* (1965). This difference in the whole material and in the young and the old group is given in table 2, which also gives the level of significance. The difference in the average size of the pupil in blue and brown eyes is larger in maximal mydriasis than in the untreated eye. From this follows that also the *dilatation* of the pupil (the difference between the maximal and the resting size) is larger in blue than in brown eyes. This is in accordance with the results of *Obianwu* & *Rand* (1965) and *Gambill et al.* (1967).

In both age groups there is a slight constriction of the pupils after phenylephrine during the first 10 min. in this trial. The statistical significance of this dip in the curve has been tested by the method of paired comparison. The difference between the pupil diameter at t = 0 and t = 5 min. is found to be highly

significant in both age groups ($P<0.001$). However it can not be stated that this effect is caused by phenylephrine because in this trial there was at the same time a dilatation in the fellow eyes after cyclopentolate. This dilatation may have been the cause of a consensual pupil constriction in the eyes treated with phenylephrine in which the mydriatic effect comes later.

The change in the size of the pupil during 5 min. may be taken as a measure of the speed of the dilatation. This may be studied in fig. 4 which shows the derivative curves of those in fig. 1. It is seen that after cyclopentolate the pupil dilates most rapidly between the 5 and the 10 minute in both age groups. After phenylephrine the most rapid dilatation takes place between the 15 and the 20 minute in the old individuals, between the 25 and the 30 minute in the young ones.

Analysis of variance gives the result that in both age groups there is a positive correlation between the maximal size of the pupil after cyclopentolate and after phenylephrine (in the young group $r = +0.7451$, slope of the regression line $b = 1.67$, intercept $a = -6.50$; in the old group $r = +0.5931$, $b = 0.48$, $a = 4.65$). In the group of old individuals there is also a positive correlation between the maximal and the resting size after cyclopentolate ($r = +0.7026$, $b = 1.20$, $a = 2.47$) and after phenylephrine ($r = +0.7000$, $b = 0.96$, $a = 4.47$) while this correlation coefficient does not significantly differ from zero in the group of young individuals. Similar values are found also if only blue eyes are included in the analysis.

These calculations seem to indicate that the actual *dilatation* of the pupil (i. e. the difference between the maximal and the resting size) in the old individuals is on the whole independent of the resting size, while in young individuals

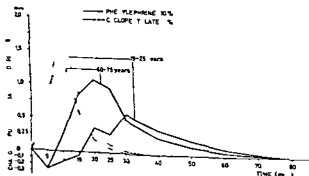


Fig. 4
The speed of dilatation of the pupil after mydriatics

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Phenylephrine old – young	7.83 – 6.79 = 1.04	P<0.001
Young group cyclopentolate – phenylephrine	7.97 – 6.79 = 1.18	P<0.001
Old group phenylephrine – cyclopentolate	7.83 – 6.67 = 1.16	P<0.001
Young cyclopentolate blue – brown	8.16 – 7.58 = 0.58	0.001<P<0.005
Young phenylephrine blue – brown	7.14 – 6.08 = 1.06	0.005<P<0.01
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material in which the average size of the pupil in the untreated eye is 4.06 mm in the young and 3.50 mm in the old individuals. The difference is highly significant (table 2).

The resting pupil is found to be on an average slightly smaller in eyes with brown iris than in eyes with blue iris. This was also found by *Obianwu & Rand* (1965). This difference in the whole material and in the young and the old group is given in table 2 which also gives the level of significance. The difference in the average size of the pupil in blue and brown eyes is larger in maximal mydriasis than in the untreated eye. From this follows that also the *dilatation* of the pupil (the difference between the maximal and the resting size) is larger in blue than in brown eyes. This is in accordance with the results of *Obianwu & Rand* (1965) and *Gambill et al.* (1967).

In both age groups there is a slight constriction of the pupils after phenylephrine *during the first 10 min in this trial. The statistical significance* of this dip in the curve has been tested by the method of paired comparison. The difference between the pupil diameter at t = 0 and t = 5 min is found to be highly

Summary

The mydriatic effect of cyclopentolate 1 % and phenylephrine 10 % has been measured in two age groups a young 19–25 years and an old 60–75 years In each subject one eye was given cyclopentolate and the other eye phenylephrine at the same time In both age groups maximal mydriasis was reached on an average 25 min after cyclopentolate, 67 min after phenylephrine In the young subjects cyclopentolate gave much better mydriasis (average of maximal values 8 0 mm) than phenylephrine (6 8 mm) while the opposite was the case in the old subjects (6 7 mm and 7 8 mm respectively) The practical importance of this is pointed out.

The different reactions in the young and the old individuals hangs probably together with senile changes in iris It is proposed that the different reactions may be explained by a weaker tonus both in sphincter and in dilatator pupillae in the old individuals as compared with the young An increased tonus in the dilatator induced by phenylephrine, will then in old individuals have a relatively strong effect while a reduced tonus in the sphincter after cyclopentolate will be less effective

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Address for reprints
M Davanger
Eye Department Rikshospitalet Oslo Norway

a *negative* correlation is found between the dilatation and the resting size. This is confirmed by further calculations, mainly after cyclopentolate, where $r = -0.5741$, $b = -0.75$, $a = 6.94$. (If only blue eyes are included $r = -0.8717$, $b = -1.03$, $a = 8.28$.) The reason for this is probably that a pupil with a large resting size can dilate relatively little before the maximal attainable size is approached.

Comments

The most significant result of this trial is the marked difference in the young and the old individuals in the effect of the two mydriatics used. Cyclopentolate has a strong mydriatic effect in the young and weak effect in the old individuals, while the opposite is the case for phenylephrine. This difference is important from a practical point of view, when the drug is given to obtain a good mydriasis for diagnostic or therapeutic purpose. The rapid effect of cyclopentolate as compared with the slower effect of phenylephrine is also remarkable. Especially in old patients it is reasonable to use both cyclopentolate and phenylephrine, as this should give both a rapid and a full mydriasis (*Priestley & Medine* 1960).

The different effect in the young and the old individuals is also interesting from a theoretical point of view, as it gives a new indication of the changes taking place in the eye with increasing age.

It does not seem probable that the different effect hangs together with different resorbtion of the drugs in the two age groups. If this were the case one would not expect the maximal mydriasis to be reached after about the same time in both groups.

It is more likely that the difference is caused by changes in iris with sphincter pupillae and dilatator pupillae. The senile miosis is probably also explained by such changes in iris.

Cyclopentolate is a cholinergic depressant, and the mydriatic effect is caused by relaxation of sphincter. Phenylephrine is a sympathomimetic drug, whose effect is caused by augmentation of the dilatator.

A possible explanation of the different effect in the two age groups is the following.

In the old individuals the tonus both of sphincter and dilatator is reduced as compared with the young. The effect of a relaxation of sphincter by cyclopentolate is then relatively smaller. On the other hand, the augmentation of tonus in the dilatator by phenylephrine induces better mydriasis, as it is not counteracted by a strong tonus in the sphincter muscle.

Ocular Rigidity *Friedenwald* (1937) (2) developed an equation which provided ophthalmic investigators with a tool for further study of the pressure volume relationship of the eye The concept which evolved here was that of the coefficient of scleral rigidity or more precisely ocular rigidity This expression denoted by k was incorporated in this the classical *Friedenwald* equation

$$k(\Delta V) = \log \frac{P}{P_0}$$

where ΔV represents the increment of change of ocular volume and P the intraocular pressure resulting when an eye of pressure P_0 has undergone such a volume change The coefficient is essentially a measure of the elasticity of the eye *Friedenwald* defined k in terms of a common logarithm Others have expressed it in natural logarithm form designating it by k_r or by E (3 4) The ocular rigidity is almost consistently found throughout the literature as a unitless number This practice should be avoided for the purpose of clarity and precision in definition and should be replaced by that which properly includes its unit of measurement μl^{-1}

Friedenwald proposed the coefficient of ocular rigidity as a constant for any one given eye Many investigators have subsequently voiced different opinions *Eisenlohr & Langham* (5) (1962) found k to differ in viable and non viable eyes with a higher value in the latter this observation they attributed to the absence of blood pressure The same authors noted that rigidity decreased slightly as the intraocular pressure increased (6) The inelastic behavior of the sclera at higher pressures has been assumed to be a probable cause (7) *McBain* (4) also showed an inverse relationship between rigidity and intraocular pressure He formulated this relationship as

$$E = M \left\{ \frac{P_1^{0.35} - P^{0.35}}{\Delta V} \right\}$$

where E represents rigidity in natural log form and M the converting factor from natural to common logarithm *McEwen & St Helen* (3) developed an empirical equation the unifying formulation of ocular rigidity to incorporate any existent fluctuations of the rigidity factor This was expressed as

$$\frac{\Delta P}{\Delta V} = aP + b$$

where a and b are constants

Clinical tonography has been based on average ocular rigidities However many human eyes have shown significantly lower or higher k values than the accepted normal of 0 0215 μl^{-1} (range 0 005–0 200 μl^{-1}) Correcting for high k values has resulted in a reduction of the calculated facility of outflow and

From the Department of Ophthalmology Medical College of Virginia Health Sciences Center Virginia Commonwealth University Richmond Virginia

THE EFFECT OF L-NOREPINEPHRINE ON THE FACILITY OF OUTFLOW IN NORMAL AND BUPHTHALMIC RABBITS

BY

VAN B NOAH JAMES L BROWN and J GEERAETS

Introduction

Many efforts have been made in recent years to discover more reliable methods of controlling glaucoma Studies regarding the influence of various pharmacologic compounds on the facility of outflow have comprised an integral part of these endeavors To determine any beneficial effects has necessitated an extensive search for an accurate comprehension of the aqueous dynamics of the eye A variety of methods have been developed to evaluate the facility of outflow itself The results of these investigations have indicated that increased intraocular pressure in the presence of glaucoma is due almost exclusively to increased resistance to aqueous outflow (1) Other factors of aqueous dynamics including rate of aqueous production systemic blood pressure coefficient of ocular rigidity and episcleral venous pressure have been extensively studied in an attempt to recognize any possible variation which might affect the facility of outflow whether it be real or apparent

This paper reviews some earlier concepts of aqueous dynamics and offers a simple and reliable method for evaluation of the effect of intracameral levarterenol or l norepinephrine on the facility of outflow in normal and buphthalmic rabbits eyes the actual topic of this paper In the subsequent text facts are mentioned which motivated the selection of this particular compound

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ice versa (8 9) In normal rabbits the average ocular rigidity determined by
linical tonography has been given as approximately 015 μl ^{1} (10)

Episcleral Venous Pressure The episcleral venous pressure P_v occasion
lly referred to as the intrascleral venous pressure comprises the lesser extreme
f the pressure gradient system across the anterior chamber angle of the eye
inner (1) (1955) described a method of measuring this pressure and with
ornbluth (10) he determined it to be approximately 8 94 mmHg in normal rab
its *Grant* (1) assumed a value of 4 mmHg for human eyes when he developed
is equation upon which clinical tonography has been based *Goldmann* (12)
stimated this value to be as high as 10 mmHg Regardless of these discrepan
es *Linner* (13) found the episcleral venous pressure in glaucoma patients to be
naffected by intraocular pressure changes

One of the advantages of manometric tonography over clinical tonography
spite of the various instruments available for this method is the minimal or
erhaps absent change in the episcleral venous pressure during the procedure
'ith the latter there is necessarily some orbital compression which could pos
bly affect the orbital venous flow

Facility of Outflow The facility of outflow C has been defined as the ratio
the flow rate of aqueous humor filtering through the trabecular meshwork to
e pressure gradient across the angle expressed in μl min $^{-1}$ mmHg^{-1} Tradi
nally it has been treated as a constant for any particular eye and has served
many years as an important criterion in the diagnosis of glaucoma although
an index it has proven itself less reliable than the P_0/C ratio Its constancy
s been disputed by several investigators in the past few years *Eisenlohr* &
ngham (5) found in rabbits maximal outflow facility values at 25 to 30 mmHg
intraocular pressure These values decreased above and below this range
ovided that the intraocular pressure did not exceed the systolic blood pressure.
the blood pressure were exceeded then C increased similarly as in dead
bit eyes *Kornbluth* & *Linner* (10) observed that the facility decreased by
ut 25 % in rabbits when the ipsilateral common carotid artery was ligated
laining this phenomenon as a homeostatic mechanism for the maintenance
he intraocular pressure whereby such a decrease in facility of outflow coun
acted the reduction of aqueous production by the ciliary body *Armaly* (14)
covered that increased intraocular pressure in rabbits and cats markedly and
nediately depressed the outflow facility but he proceeded to show that this
cess was reversible Although he demonstrated this as a linear relationship
felt that it would seriously perplex future investigations of the facility of
flow Results of our own investigations confirmed the findings reported by
author

he manometric decay curve of aqueous outflow has been recognized as ex
ential The initially fast decline in pressure has not yet been satisfactorily
lained *St Helen* & *McEwen* (7) were able to break up this curve into two

components the fast and the slow relaxation curves and proposed time to be a parameter partially responsible for this phenomenon They also felt that the inelasticity of the sclera under strain was a probable answer *Moses* (9) in his discussion of the errors of clinical tonography suggested that this fast drop *during* the first *minute* might represent a decrease in ocular blood volume or a slow stretching of the ocular coats The fact has remained however that a good normal clinical *tonogram does have a gentle upward concavity"* thereby in validating to a slight degree the linear nature of the classical *Grant* equation (1)

$$C = \frac{\Delta V}{4(P_{a\,t} - P \;- 1\,25)}$$

Irmaly (15) checked the minute by minute consistency of this negative exponential decay curve of clinical tonography and discovered that the straight line was not a *satisfactory* approximation of the first four minute segment *McEwen et al* (16) supported *Grant* (1) by integrating this equation over the entire interval of four *minutes finding* that their C values differed insignificantly from those in the currently used tables In addition they designed an electrical ocular model which did not *provide results far different from* the C tables of *Friedenwald* although it did tend to strengthen the concept of viscoelasticity of the eye in opposition to the classical *Friedenwald* model (17)

The mean facility of outflow of normal rabbits was determined by the clinical tonographic studies of *Kornbluth & Linner* (10) as 0 30 μl *min* $^{-1}$ *mmHg*$^{-1}$ with an average intraocular pressure *of* 23 mmHg *Sears* (18) ascertained this value by perfusion techniques as 0 24 μl min^{-1} mmHg^{-1} *Becker & Constant* (19) found by both clinical and manometric tonography consistent values of C in living and dead rabbit eyes Their average C value was 0 35 μl min $^{-1}$ mmHg^{-1} with a mean intraocular pressure of 19 mmHg *McMaster* (20) used perfusion techniques and determined this C value to be 0 10 μl min $^{-1}$ mmHg^{-1} for buphthalmic rabbits *All* were in agreement that the rabbit eye behaved *similarly to* that of the human in spite of the anatomically *different* outflow systems

Pseudofacility Pseudofacility was defined by *Barany* (21) (1963) as the decrease *in* net inflow of aqueous humor into the eye occurring with an increase in intraocular pressure He based his *definition* on the fact that such an increase in pressure *could* inhibit aqueous production and thereby give the *impression of* a facility of outflow somewhat higher than its true value *Barany* integrated the infinitesimal vascular *components* within the eye with regard to their various *parameters* by utilizing data from previous *investigations of the* relationship between intraocular pressure and blood pressure (22 23) From this mathematical model he derived an approximation of pseudofacility in rabbits as 10 • , of the true facility *Kupfer & Sanderson* (24) by varying the episcleral venous pressure in human subjects with a neck pressure cuff ascertained this relationship as Pseudofacility = Total facility $\times$ $(1 - \Delta P / \Delta P\ )$

where ΔP_t is the change in intraocular pressure and ΔP_v the change in the episcleral venous pressure The average pseudofacility was 21 % of the mean total facility Later studies by *Barany* (25) showed similar results *Langham* (26) determined in rabbits that moderate increases in intraocular pressure either decreased aqueous production or enhanced outflow facility or a combination of the two by a factor of 50 % A similar result of 52 % was found by *Langham Eisenlohr & Maumenee* (6) three years later Their conclusion was that some of the aqueous outflow must have actually been an efflux of blood from the intraocular vascular compartments *Macri* (27) used anesthestized cat eyes to demonstrate approximately an 8 % decrease in aqueous formation for every mmHg rise in intraocular pressure *Langham & Eisenlohr* (28) found evidence for a more significant aqueous suppression in relation to minor increase in the intraocular pressure when the eye approached steady state conditions *Becker & Friedenwald* (29) used the fluorophotometric method of *Goldmann* (30) to find that clinical tonography had neither mechanical nor reflexive effects on the secretory or diffusion mechanisms of the eye They pointed out however the lack of accuracy in their method

Anatomical Considerations The buphthalmic rabbit has lent itself to rather extensive ocular investigations A recessive autosomal gene with varying penetrance has been found to be responsible for the buphthalmos (31) The development of glaucoma in these rabbits has been described (32) These eyes have shown various degrees of enlargement with generally deep anterior chambers. The glaucoma was believed to be due to a greater resistance to outflow *Greaves & Perkins* (33 (1951) were unable to demonstrate any aqueous veins following injection of *Evans* blue dye into the anterior chamber under normal pressure conditions but were able to see the dye in the episcleral venous plexus when the injection was made under a pressure of at least 80 mmHg This abnormally poor aqueous drainage system has apparently resulted in the consistently present highly elevated intraocular pressures *McMaster* (20) (1960) found by histologic studies a wide and fibrotic angle *Lee* (34) (1969) could not confirm this explanation on the basis of his own gonioscopic and histologic examinations but rather could only demonstrate undifferentiated uveal tissue in the angle *Lee* also felt that there was underdevelopment rather than atrophy of the ciliary body probably as a result of decreased aqueous formation He assumed that abnormal insertion of the uveal tissue anteriorly was responsible for the incomplete cleavage of the angle with absence of the space of Fontana and malformation of the outflow channels

In a general study of outflow *Fowlks & Havender* (35) (1964) labeled the aqueous of normal albino rabbits with nitroblue tetrazolium chloride and followed its exit through the ciliary cleft into the perivascular spaces and aqueous channels of the ciliary body noting some evidence of communication with the suprachoroid Unexpectedly there was no observed exit through the trabecular

meshwork *Bill* (36) (1965) *found that uveoscleral routes accounted for 20 % of* aqueous outflow in monkeys Another route was discovered in enucleated human eyes by *François et al* (37) (1967) They followed thorotrast with microradiolo gical techniques to discover a canalicular network within the iris which led to the venous plexus of the ciliary body pars plana choroid and sclera

Holland et al (38) (1957) studied the innervation of the trabecular meshwork of rabbits and found nerve endings from three sources – the parasympathetic and sympathetic systems and the fifth cranial nerve These endings were de monstrated by optico ciliary neurotomy (total denervation to the eye) ciliary ganglionectomy trigeminal neurotomy and superior cervical ganglionectomy in decreasing proportions respectively

Relationship between aqueous dynamics and the adrenergic mechanism

Jaffe (39) (1948) observed that post ganglionic sympathectomy in the cat re duced the intraocular pressure on the ipsilateral side for several weeks after wards whereas pre ganglionic extirpation did not produce this effect His po stulate was that this decrease was due to reduced tonus of the non striated muscles of the eye *Linner & Prijot* (40) (1955) observed a 50 % decrease in intraocular pressure on the first day following superior cervical ganglionectomy in rabbits but saw no change in the facility of outflow The pressure was re stored to normal levels by the second postoperative day They concluded that the adrenergic mechanism was involved in aqueous secretion *Lieb Guerry & Ellis* (41) (1958) confirmed these findings *Langham & Taylor* (42) (1960) used the fluorophotometric method to show that the rate of aqueous production was not affected With perfusion techniques they demonstrated an increase in the outflow facility without a change in the episcleral venous pressure In addition they observed an increase in blood flow through the eye and they noted that post ganglionic sectioning in rabbits caused a gradual decrease in the steady state intraocular pressure with a maximum effect at 24 hours and a return to normal by three to four days (43) The same effect was not observed by them when pre ganglionic sectioning was performed *Sears & Barany* (44) (1960) in fused separately into the anterior chamber the alpha receptor blocker Dibena mine and the beta receptor blocker dichloroisoproterenol (DCI) and observed respectively a decrease and an increase in the facility From these observations he interpreted the effect of ganglionectomy to be caused by a concomitant loss of adrenergic beta activity from chromaffin cells and excessive release of alpha active mediators from the degenerating nerve endings *Barany* (45) (1962) ex

perimented with various pharmacologic agents and observed that systemic but not intracameral administration of reserpine and guanethidine prior to ganglionectomy blocked its effect He discovered that phenoxybenzamine and Dibenamine, both alpha receptor blockers interfered with the ganglionectomy effect only if administered intracamerally whereas phentolamine an alpha receptor blocker with better penetrability blocked the effect systemically as well Topical DCI increased the facility of outflow as did also systemic administration Pre treatment with systemic Dibenamine prevented the systemic influence of DCI Combined pretreatment with both DCI and Dibenamine did not significantly reduce the ganglionectomy effect. His conclusion was that ganglionectomy did indeed release into the aqueous from the iris and ciliary body an alpha active adrenergic agent which had some direct but unknown influence on the trabecular meshwork resulting in an increase in the facility of outflow

Eakins (46) (1963) made separate intravitreal injections of l norepinephrine an almost pure alpha adrenergic agent isoproterenol an almost pure beta adrenergic agent and l epinephrine an adrenergic agent with properties of both He found that l norepinephrine reduced the intraocular pressure by increasing the facility of outflow l epinephrine also by increasing the facility but in addition by reducing the rate of aqueous production and isoproterenol only by reducing the production Isoproterenol reduced the pressure the least of the three drugs *Eakins* & *Eakins* (47) (1964) assayed the catecholamine content of the ocular tissues of rabbits and found the iris and the ciliary body to contain the highest concentrations especially of l norepinephrine Postganglionic sympathectomy caused depletion of these catecholamines in 24 hours whereas preganglionic sympathectomy resulted in no change thus lending support to the conclusions of *Barany* In addition they determined no change in the aqueous concentrations with prolonged stimulation of the sympathetic system Pretreatment with cocaine increased the aqueous catecholamine concentration supporting the theory that cocaine is an antagonist of the normal uptake of endogenous l norepinephrine by tissue stores *Sears* & *Gillis* (48) (1967) observed a progressive decline in the degree of retention of intravenously-administered l norepinephrine by the iris 24 hours following ganglionectomy *Sears et al* (49) (1966) found that the facility of outflow was directly proportional to the concentration of l norepinephrine in the ocular tissues after 24 hours and they further determined that bilateral sympathectomy had more effect on C as well as a longer duration of the depletion of tissue l norepinephrine

The trabeculum of an eye following sympathetic denervation has been shown to become more sensitive to l norepinephrine *Sears* & *Sherk* (50) (1964) demonstrated this phenomenon with their discovery that one week following ganglionectomy the facility of outflow increased significantly with intravitreal and subconjunctival administration of l norepinephrine and markedly so with intracameral injection Their feeling was that the site of action was probably

intrascleral *Langham* (51) (1965) observed in such hypersensitive eyes the drop in intraocular pressure and the dilatation of the pupil occurring with administration of l norepinephrine to be blocked by intravenous phenoxybenzamine In addition the pressure lowering effect of isoproterenol was blocked by propanolol a beta receptor blocker His results suggested that both the alpha and beta receptors acted to decrease intraocular pressure but that only alpha receptors acted to contract the dilator muscle of the iris

Propanolol has been currently investigated as a potential drug in treating glaucoma (52 53 54) It has been shown to reduce the intraocular pressures of normal eyes and more remarkedly the pressures of eyes with open angle glaucoma when administered topically orally and intravenously It has not influenced significantly eyes with congenital glaucoma. Its mode of action has been postulated as that of increasing the facility of outflow and of reducing the aqueous production by a lowering of the blood pressure Unlike DCI it has not demonstrated any intrinsic beta activity

Barany & Gassmann (55) (1965) published data which suggested that the effect of ganglionectomy was independent of the blood circulation but which implied that the mechanism of the increase in facility was identical with that occurring with the interruption of the systemic circulation *Casey* (56) (1966) caused an average 5 μl decrease in intraocular volume by electrical pulsatile stimulation of the sympathetic system presumable due to intraocular vasoconstriction. He also observed a 10–20 % reduction in the facility of outflow not blocked by phentolamine or atropine He therefore postulated either a direct effect on the trabeculum or the presence of specialized adrenergic ciliary muscle fibers

Barany (?5) (1968) determined that l epinephrine affected the pseudofacility more significantly when the true facility was low in value suggesting some possible influence upon the posterior uveoscleral outflow routes *Bill* (57) (1969) felt that any reduction in outflow by l epinephrine was due to relaxation of the ciliary muscle and that any increase in outflow by this drug was due to its direct influence on the endothelium of the canal of Schlemm. *Willetts* (58) (1969) showed that topical l epinephrine and l norepinephrine neither caused mydriasis nor increased the facility of outflow in normal human eyes

Derivation of equation for evaluating manometric decay curves

The derivation of a useful mathematical expression of the manometric decay curve (see Figure 1) assumes the validity of the previously mentioned *Friedenwald* equation

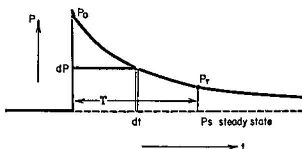


Figure 1
Schematic manometric decay curve

$$k(\Delta V) = \log \frac{P}{P_0}$$

in spite of the fact that other mathematical models have been proposed The authors feel this equation to be satisfactorily accurate for the purpose of comparing the effects of drugs on the same eyes However in this paper the *Friedenwald* equation has been modified to a form more suitable for mathematical manipulation

$$P = P_s e^{kv}$$

where the steady state pressure P_s replaces P_0 as the arbitrary baseline pressure v supersedes ΔV with identical definition for the sake of symbolic simplicity, and k now represents the ocular rigidity in natural logarithm form This k value is more than twice the conventional *Friedenwald* value ($\ln X = 2.303 \log X$) but does not change its concept since the relationship between the two is linear The ocular rigidity is assumed to remain essentially constant within the pressure ranges utilized in this investigation The steady state pressure becomes an important value in determining the facility of outflow by the method now being described Even in clinical tonography it is of consequence taking its form as the initial pressure instead of that value approached here by the decaying curve (59)

The second equation assumed valid in this derivation is the hydrodynamic formulation of *Poiseuille* (60)

$$\Gamma = \frac{\pi r^4}{8\eta l} (P_1 - P)$$

This equation quantitates the rate of flow Γ of a fluid of viscosity η through a tubular system of radius r and length l over a pressure gradient of $(P_1 - P)$ If the filtration of aqueous through the angle is considered to occur through thousands of microtubular structures summated over 360° the *Poiseuille's* equation can be ocularly modified to become

$$F = C(P - P_v)$$

where F is the rate of aqueous outflow P the variable intraocular pressure, P_v the episcleral venous pressure, and C a constant called the facility of outflow This equation is identical to that used by other investigators in their formulations (17 28 60) *If the eye is at steady state then* $P = P_s$ and $F_s = Q$ where Q is the constant rate of aqueous production (it is assumed here that Q does not vary significantly with changes in the intraocular pressure) Hence $Q = F_s = C(P - P_v)$ Then,

$$\text{Rate of decay} = \frac{dv}{dt} = Q - F$$

or

$$\frac{dv}{dt} = C(P - P\ ) - C(P - P\ )$$

or

$$\frac{dv}{dt} = -C(P - P\ )$$

Therefore the episcleral venous pressure which is also assumed to vary insignificantly does not remain an essential entity in this derivation. If v is replaced by $\frac{1}{k} \ln \frac{P}{P_s}$ (from the *Friedenwald* equation) then

$$\frac{d(l/k \ln P/P\ )}{dt} = -C(P - P\ )$$

$$\frac{dP}{P(P - P\ )} = -kC\,dt$$

Integrated within the proper limits ($P = P$ when $t = 0$ and $P = P_T$ when $t = T$) the above equation becomes

$$\int_{P}^{P_t} \frac{dP}{P(P - P\ )} = -kC \int_{0}^{T} dt$$

or

$$\frac{1}{P} \ln \left\{\frac{1 - P/P_T}{1 - P/P0}\right\} = -kCT$$

and finally

$$C = \frac{1}{P_s}\frac{1}{kT} \ln \left\{\frac{1 - P_s/P_0}{1 - P_s/P_T}\right\}$$

This equation yields a value for the facility of outflow easily obtained by merely selecting two representative points on the decay curve separated by a

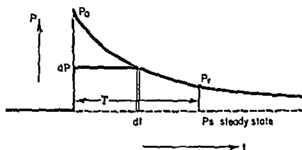


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$$\text{Rate of decay} = \frac{dv}{dt} = Q - F$$

or

$$\frac{dv}{dt} = C(P - P\ ) - C(P - P_v)$$

or

$$\frac{dv}{dt} = -C(P - P_s)$$

Therefore the episcleral venous pressure which is also assumed to vary insignificantly does not remain an essential entity in this derivation If v is replaced by $\frac{1}{k}\ln\frac{P}{P}$ (from the *Friedenwald* equation) then

$$\frac{d(l/k \ln P/P\ )}{dt} = -C(P - P\ )$$

$$\frac{dP}{P(P - P\ )} = -kC\,dt$$

Integrated within the proper limits ($P = P_0$ when $t = 0$ and $P = P_T$ when $t = T$) the above equation becomes

$$\int_{P}^{P_t} \frac{dP}{P(P - P\ )} = -kC \int_{0}^{T} dt$$

or

$$\frac{1}{l}\ln\left\{\frac{1 - P\ /P_T}{1 - I_s/P0}\right\} = -kCT$$

and finally

$$C = \frac{1}{P_s}\frac{1}{kT}\ln\left\{\frac{1 - P_s/P_0}{1 - P\ /P_T}\right\}$$

This equation yields a value for the facility of outflow easily obtained by merely selecting two representative points on the decay curve separated by a

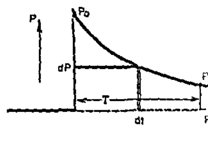


Figure 1
Schematic manometric de

$$k(\Delta V) = \log \frac{P}{P_t}$$

in spite of the fact that other mathematical mo authors feel this equation to be satisfactorily acc paring the effects of drugs on the same eyes *Friedenwald* equation has been modified to a form tical manipulation

$$P = P_s e^{kv}$$

where the steady state pressure P_s replaces P_0 as the v supersedes ΔV with identical definition for the and k now represents the ocular rigidity in natural lo is more than twice the conventional *Friedenwald* v but does not change its concept since the relationship The ocular rigidity is assumed to remain essentially c ranges utilized in this investigation The steady stat portant value in determining the facility of outflow described Even in clinical tonography it is of conse the initial pressure instead of that value approach curve (59)

The second equation assumed valid in this derivat formulation of *Poiseuille* (60)

$$F = \frac{\pi r^4}{8\eta l} (P_1 - P_o)$$

This equation quantitates the rate of flow F of a flui a tubular system of radius r and length l over a pressu If the filtration of aqueous through the angle is consi thousands of microtubular structures summated over 360 tion can be ocularly modified to become

$$F = C(P - P_v)$$

where F is the rate of aqueous outflow P the variable intraocular pressure P the episcleral venous pressure and C a constant called the facility of outflow This equation is identical to that used by other investigators in their formulations (17 28 60) If the eye is at steady state then $P = P_s$ and $F_s = Q$ where Q is the constant rate of aqueous production (it is assumed here that Q does not vary significantly with changes in the intraocular pressure) Hence $Q = F_s = C(P_s - P\ )$ Then,

$$\text{Rate of decay} = \frac{dv}{dt} = Q - F$$

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Therefore the episcleral venous pressure which is also assumed to vary insignificantly does not remain an essential entity in this derivation If v is replaced by $\frac{1}{k} \ln \frac{P}{P_s}$ (from the *Friedenwald* equation) then

$$\frac{d(1/k \ln P/P\ )}{dt} = -C(P - P\ )$$

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Integrated within the proper limits ($P = P_o$ when $t = 0$ and $P = P_T$ when $t = T$) the above equation becomes

$$\int_{P}^{P_t} \frac{dP}{P(P - P\ )} = -kC \int_{0}^{T} dt$$

or

$$\frac{1}{I} \ln \left\{\frac{1 - P\ /P_T}{1 - P_s/P0}\right\} = -kCT$$

and finally

$$C = \frac{1}{P_s} \frac{1}{kT} \ln \left\{\frac{1 - P_s/P_O}{1 - I_s/P_T}\right\}$$

This equation yields a value for the facility of outflow easily obtained by merely selecting two representative points on the decay curve separated by a

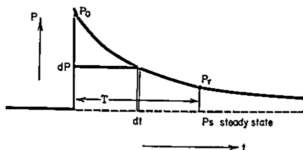


Figure 1
Schematic manometric decay curve

$$k(\Delta V) = \log \frac{P}{P_o}$$

in spite of the fact that other mathematical models have been proposed The authors feel this equation to be satisfactorily accurate for the purpose of comparing the effects of drugs on the same eyes However in this paper the *Friedenwald* equation has been modified to a form more suitable for mathematical manipulation

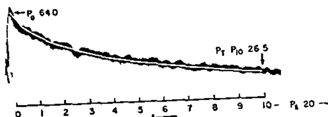
$$P = P_s e^{kv}$$

where the steady state pressure P_s replaces P_o as the arbitrary baseline pressure v supersedes ΔV with identical definition for the sake of symbolic simplicity and k now represents the ocular rigidity in natural logarithm form This k value is more than twice the conventional *Friedenwald* value ($\ln X = 2\ 303 \log X$) but does not change its concept since the relationship between the two is linear The ocular rigidity is assumed to remain essentially constant within the pressure ranges utilized in this investigation The steady state pressure becomes an important value in determining the facility of outflow by the method now being described Even in clinical tonography it is of consequence taking its form as the initial pressure instead of that value approached here by the decaying curve (59)

The second equation assumed valid in this derivation is the hydrodynamic formulation of *Poiseuille* (60)

$$\Gamma = \frac{\pi r^4}{8\eta l} (P_1 - P_o)$$

This equation quantitates the rate of flow Γ of a fluid of viscosity η through a tubular system of radius r and length l over a pressure gradient of ($P_1 - P$) If the filtration of aqueous through the angle is considered to occur through thousands of microtubular structures summated over 360° the *Poiseuille s* equation can be ocularly modified to become



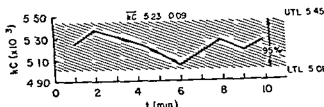


Figure 2
Statistical analysis – Tolerance test of the fit of a typical manometric decay curve with the decay equation.

Material and methods

Six normal adult albino New Zealand rabbit eyes and 17 moderate to severe buphthalmic eyes from the AXbubu strain were used The buphthalmic rabbits were obtained from The Jackson Laboratory in Bar Harbour Maine Each normal rabbit was anesthetized with 1 2–1 7 gm/kg of 25 % urethane Buphthalmic rabbits required less 1 1–1 3 gm/kg The urethane was administered intravenously over about 15 minutes The hair around the involved eye was sheared and the area prepped with an iodine alcohol solution Both upper and lower lids were then infiltrated with 4 % procaine and retracted with 4–0 silk sutures to minimize any possible external pressure on the globe Pontocaine solution 0 5 % was instilled into the cul de sac of the eye The rabbit was laid on its side with its head extended fully to reduce respiratory problems A 23 gauge disposable needle attached securely to a 3 inch polyethylene tubing was inserted into the anterior chamber its tract being interlamellar for a short distance before penetrating Descemet s membrane The other end of the tubing was connected to a three way stopcock which in turn was attached to a Sanborn 267 BC

time T, deciding upon the proper steady state pressure and substituting these values in the equation itself It agrees well with an equation derived by *Fox* (61) who analyzed pressure decay curves under varying assumptions

A more useful form of the above equation is

$$kC = \frac{1}{P_s}\,\frac{1}{T}\,\ln\left\{\frac{1-\dfrac{P_s}{P_t}}{1-\dfrac{P_s}{P_T}}\right\}$$

This equation emphasizes the product kC rather than the facility of outflow *per se* This version finds use in this paper since it more accurately compares decay curves before and after intracameral injections of drugs thereby eliminating the necessity of experimentally determining k with its accompanying experimental error The product kC has no real physical significance and is therefore useless in comparing the decay curves of one eye against those of another

If integration is performed from (0 P_0) to (t P) then the resulting equation can be used to check the fit of any applicable decay curve (See Figure 2 and Table 1) Here all values of kC are seen to fall within the 95 % tolerance limits. Other curves tested showed equally good fits

Table 1

Data for tolerance fit of decay curve in Fig 2

t (min)	P (mmHg)	kC ($mmHg^{-1}$ min^{-1})
1	52.0	5.25×10^{-3}
2	45.0	5.37
3	40.0	5.30
4	36.5	5.25
5	34.5	5.15
6	32.0	5.05
7	30.0	5.18
8	28.5	5.27
9	27.5	5.18
10	26.5	5.27

transducer The other inlet to the transducer housed a 1 cc plastic tuberculin syringe containing a reservoir of normal saline The transducer fed into a Sanborn 150–3000 pre amplifier built within a Sanborn 150 console with an accompanying Sanborn 158–100B polygraph recorder (62) The needle of a Hamilton microliter syringe was also inserted into the anterior chamber in a manner similar to that of the transducer needle and was balanced so as not to distort or compress the globe This syringe contained 5 μg of l norepinephrine (Levarterenol bitartrate) for normal rabbits and 15 μg for buphthalmic rabbits since the anterior chamber volume of the latter has been determined to be about three times that of the former (63)

After the needles were inserted at least 15 minutes were allowed to elapse until the intraocular pressure again reached steady state conditions Saline from the syringe reservoir was then injected into the anterior chamber in volume sufficient to raise the intraocular pressure by 20 to 30 mmHg This pressure was allowed to decay steady state One or two more curves were monitored Next the l norepinephrine was injected and 20 to 30 minutes allowed to pass Two or three post injection decay curves were recorded and the experiment terminated. It was desirable that these decay curves be contained within the limits of 20 and 50 mmHg

More saline was required to adequately raise the pressure in the buphthalmic eyes because of their lower scleral rigidities and larger anterior segment volumes Usually from 10 to 20 μl were required for normal eyes and from 40 to 60 μl for buphthalmic eyes These volumes were not necessarily recorded

The kC values were determined for all curves All pre injection values were averaged for a single eye as were the post injection values These mean results were then statistically analyzed

Results

The kC values for the decay curves before and after injection of l norepinephrine are shown for normal and buphthalmic rabbits in Tables 2 and 3 respectively Statistically analysis by means of paired t testing shows that the probability of accepting the null hypothesis is 0 0008 for normal rabbits and 0 48 for buphthalmic rabbits The null hypothesis states that l norepinephrine does not increase the kC value It can be safely stated then that intracameral l norepinephrine increases the facility of outflow in normal rabbits (by about 75 %) but has no effect on that of buphthalmic rabbits

In this study no consideration toward pseudofacility is shown The reason is that any such factor if it does exist, need not be included since only comparison of decay curves is made in the same eye thus essentially eliminating its significance

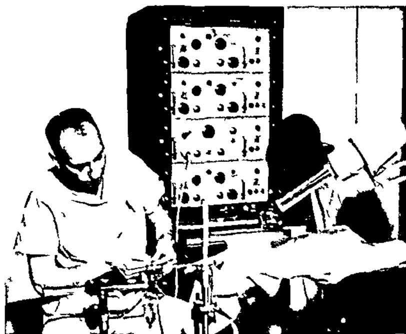


Figure 3 (a)
Overall view of the Sanborn instrumentation

Figure 3 (b)
Close up view of the transducer and manometric apparatus

Discussion

In consideration of the facts discussed in this paper the findings reported here would not be unexpected These data tend to indicate that the buphthalmic rabbit eye possesses essentially a functionless trabeculum

The manner of evaluating the decay curves in this report differs from the slope method of *Langham* (5) although the assumptions are generally the same i e that ocular rigidity episcleral venous pressure and rate of aqueous production are all essentially constant for any one given eye The advantage of the equation method used here is that (1) it quickly gives a decay value (2) it allows the investigator more freedom in selecting points on the curve that are most representative of the trend of the decay (3) it does not require any statistical analysis such as the method of least squares (4) it is more adaptable to the salvaging of data from an artefactitious curve (5) it does not require elaborate equipment and (6) it does not necessitate the determination of the ocular rigidity and thereby eliminates additional experimental error Also any rigidity factor from the polyethylene tubing is assimilated by the data and therefore does not need to be considered

One disadvantage of the equation method is that the value of the steady state intraocular pressure is required for the determination of kC Usually this value is easily obtained In some instances it has to be approximated In such a case avoidance of any large error in determining kC requires that the selection of the value of P_T be not too close to P i e the late portion of the decay curve would best be excluded when determining a value for kC

The phenomenon of pseudofacility is not considered in this method To repudiate it is not reason for its exclusion for it is assumed to exist to a certain degree But its influence is essentially cancelled in the comparisons of the decay curves Also it can be shown that the equation derived here fits the curves reasonably well without taking pseudofacility into account

As previously mentioned 1 norepinephrine does not appear to alter the rate of aqueous production because of its lack of beta activity If such an effect does exist it can be accounted for by using the resultant lower values of P in evaluating subsequent curves A depression of P might also occur with an increase in the facility of outflow Here again this new value of P should be used in determining the kC value of the accompanying curve

A method employing continuous infusion of saline into the eye did not appear to be practical for in evaluating intracameral pharmacologic effects the drug itself would also have to be infused

Barany (64) has discussed the error of the constant infusion method It was his feeling that the facility of outflow might vary during the experiment

Urethane provided adequate anesthesia in most cases No study of the effect of this agent on intraocular pressure was made *Sears* (65) (1960) has claimed

Table 2

Results of the effect of l norepinephrine on the kC product in 6 normal rabbit eyes with accompanying paired t testing

Rabbit Number	Date of Experiment	$\overline{kC}$ (before drug)	$\overline{kC}$ (after drug)	$\Delta kC = (\overline{kC}) - \overline{kC}$	Percent Change	$\Delta kC - \overline{\Delta kC}$	$(\Delta kC - \overline{\Delta kC})^2$
B-263-OS	2-17-69	0 0054	0 0086	0 0032	59 3	0 0006	0 0036×10-4
B-647-OD	2-24-69	0 0054	0 0070	0 0016	29 6	0 0022	0 0484
B-637-OS	2-11-69	0 0146	0 0217	0 0071	48 6	0 0033	0 1089
B-048-OD	2-12-69	0 0036	0 0061	0 0025	69 6	0 0013	0 0169
B-264-OD	2-18-69	0 0036	0 0071	0 0035	97 2	0 0010	0 0100
B-260-OD	3-03-69	0 0034	0 0080	0 0046	135 5	0 0008	0 0064

$$\sum_{i}^{6}(\Delta kC)_i = 0\ 0225 \qquad \sum_{i}^{6}(\Delta kC - \overline{\Delta kC})_i^2 = 0\ 1947 \times 10^{-4}$$

$$\overline{\Delta kC} = \frac{\sum_{i}^{n}(\Delta kC)_i}{n} = \frac{0\ 0225}{6} = 0\ 0038$$

$$s_{\overline{\Delta kC}} = \sqrt{\frac{\sum_{i}^{n}(\Delta kC - \overline{\Delta kC})_i^2}{n-1}} = \sqrt{\frac{0\ 1947 \times 10^{-4}}{5}} = 0\ 0020$$

$$t_{n-1} = t_5 = \frac{\overline{\Delta kC}}{s_{\overline{\Delta kC}}/\sqrt{n}} = \frac{0\ 0038}{0\ 0020\ /\sqrt{6}} = 4\ 65$$

$P[\mu\ \Delta kC = 0] = 0\ 008$ Reje t the h yp the fo the f ve cent g f ca e level

$$\overline{\Delta kC} = \frac{\sum_{1}^{n} (\Delta kC)}{n} = \frac{0\,00?)}{17} = 0\,0007$$

$$s_{\overline{\Delta kC}} = \sqrt{\frac{\sum_{1}^{n} (\Delta kC - \overline{\Delta kC})^2}{n-1}} = \sqrt{\frac{0\,1887 \times 10^{-4}}{16}} = 0\,0011$$

$$t_{\ 1} = t_{16} = \frac{\overline{\Delta kC}}{s_{\overline{\Delta kC}} / \sqrt{n}} - \frac{0\,0002}{0\,0011 / \sqrt{17}} = 0\,75?$$

Accept the null hypothesis for the five percent significance level

I {/ $\Delta kC = 0] = 0\,48$

Table 3

Results of the effect of l norepinephrine on the kC product in 17 buphthalmic rabbit eyes with accompanying paired t testing

Rabbit Number	Date of Experiment	$\overline{kC}$ (before drug)	$(\overline{kC})$ (after drug)	$\Delta kC = (\overline{kC}) - \overline{kC}$	Percent Change	$\Delta kC - \overline{\Delta kC}$	$(\Delta kC - \overline{\Delta kC})^2$
73315-OD	2-13-69	0.0032	0.0021	-0.0011	-34.4	0.0013	0.0169×10⁻⁴
75196-OD	3-06-69	0.0020	0.0012	-0.0008	-40.0	0.0010	0.0100
73310-OS	3-07-69	0.0027	0.0013	-0.0014	-52.0	0.0016	0.0256
74180-OD	3-10-69	0.0024	0.0028	0.0004	16.6	0.0002	0.0004
75196-OS	3-13-69	0.0054	0.0031	-0.0023	-42.6	0.0025	0.0225
71635-OS	4-18-69	0.0054	0.0059	0.0005	9.3	0.0003	0.0009
71635-OD	4-25-69	0.0107	0.0109	0.0002	1.9	0.0000	0.0000
71720-OD	5-16-69	0.0049	0.0057	0.0008	16.3	0.0006	0.0036
84843-OS	6-06-69	0.0068	0.0078	0.0010	14.7	0.0008	0.0064
84843-OD	7-02-69	0.0035	0.0052	0.0017	48.6	0.0015	0.0225
73802-OD	6-13-69	0.0027	0.0023	-0.0004	-14.8	0.0006	0.0036
84365-OD	6-16-69	0.0052	0.0046	-0.0006	-11.5	0.0008	0.0064
72924-OD	6-17-69	0.0030	0.0031	0.0001	3.3	0.0001	0.0001
84448-OD	6-25-69	0.0057	0.0067	0.0010	17.5	0.0008	0.0064
73906-OS	6-27-69	0.0056	0.0055	-0.0001	-1.8	0.0003	0.0009
82326-OD	7-09-69	0.0055	0.0077	0.0022	40.0	0.0020	0.0400
74520-OD	7-11-69	0.0053	0.0070	0.0017	32.1	0.0015	0.0225
				$\sum_{1}^{17} (\Delta kC)_i = 0.0029$			$\sum_{1}^{17} (\Delta kC - \overline{\Delta kC})^2 = 0.1887 \times 10^{-4}$

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that the intraocular pressure is not affected He was suppported in this regard by *Langham* (26) *Marre* (66) (1968) disagreed, feeling that there was a significant drop in the intraocular pressure as well as an increase in the facility of outflow On the other hand there has been little doubt as to the importance of Pontocaine in ocular manometry as the trigeminal reflex is adequately blocked by this topical anesthetic (65) Pontocaine *per se* has no effect on the intraocular pressure

Summary

1 A basic review of aqueous dynamics pertinent to this investigation was presented as well as a discussion of the relationship between aqueous dynamics and adrenergic mechanisms

2 A simple equation method of evaluating decay curves was presented and discussed

3 The effects of intracameral l norepinephrine on the facility of outflow of normal and buphthalmic rabbit eyes were determined This agent was found to significantly increase the facility in the normal rabbits but not to influence it in the buphthalmic rabbits

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From the Department of Ophthalmology Medical College of Virginia Health Sciences Division Virginia Commonwealth University Richmond Virginia

THE EFFECT OF ASCORBIC ACID ON THE FACILITY OF OUTFLOW IN NORMAL AND BUPHTHALMIC RABBITS

BY

VAN B NOAH and WALTER J GEERAETS

Introduction

In the past decade some interest has been shown toward the possible use of ascorbic acid as a tension lowering agent in glaucoma This concept arose with the discovery of the presence of mucopolysaccharides within the trabecular meshwork of the eye for it had been well known that ascorbic acid was essential for the syntheses of glucuronic acid a constituent of hyaluronic acid and in addition that it acted as a spreading factor by depolymerizing hyaluronic acid (1) The fact that the normal concentration of ascorbic acid in the aqueous humor was extraordinarily high ten to twenty times that in the serum also motivated research in this field

Clinical and laboratory investigations of the tension lowering effect of ascorbic acid have generally been favorable however they have not been conclusive in demonstrating the mechanism of action *Virno et al* (2) (1967) were most optimal when they reported that oral administration (0 5 Gm/Kg body weight daily) significantly decreased the intraocular pressure in both normal and glaucomatous eyes Indeed with ascorbic acid they were able to normalize pressures that had been uncontrolled by miotics and carbonic anhydrase inhibitors Mo

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schini (3) (1968) & *Bietti* (4) (1967) also observed a significant *reduction in the* intraocular pressure with high dosages of parenteral ascorbic acid they both attributed this effect to a change in *the osmotic* pressure across the blood aqueous barrier which resulted in decreased aqueous production *Missiroli & Geraldi* (5) (1965) used rabbits to show *that* the decrease in *intraocular pressure* following oral administration of ascorbic acid was directly proportional to the dosage and therefore to the aqueous concentration *Linner (6) (1966) showed* there to be a 2–3 mm Hg drop in pressure in normal eyes after 24 to 48 hours which however was only apparent with applanation *tonometry* He found no *influence from the drug* when a Schiotz tonometer was employed The conclusion that followed was the possibility that ascorbic acid *might cause* an increase in the *ocular rigidity In addition* he determined there to be a *15*% increase in the facility of outflow and a decrease in the rate of production of aqueous humor According to this author the most likely *explanation for the greater part of the* decrease in intraocular tension was a reduced rate of aqueous flow *Su u ki* (7) (1966) agreed but he found no influence by ascorbic acid *on the facility* of outflow *In a later study Linner* (8) (1969) used human eyes with borderline tensions to show a 1 1–1 2 mm Hg decrease in the intraocular pressure after six days of treatment Again he felt that a reduction in the rate of aqueous flow was mainly responsible for this effect and this time he observed no influence on the facility of outflow

Topical solutions of 10% ascorbic acid have been shown to be as effective as the oral route (7 8) Contrarily *Gnaedenger & Willome (9) (1968) showed* by statistical analysis *no significant* change in the intraocular pressure or in the facility of outflow with topical drops in normal human eyes

It has been felt that a close *relationship* among endocrine balance, sugar metabolism ascorbic acid and mucopolysaccharides existed (1) Linner (10) (1964) showed that two grams of ascorbic acid daily *offered* protection against the increased intraocular pressure occurring with long term topical steroid therapy

As no previous studies involving *ascorbic* acid have been performed on buphthalmic eyes this *investigation* attempts to determine any possible influence of intracameral administration of this drug on buphthalmic rabbit eyes using normal rabbit eyes as a control

Material and methods

The technique and method adopted for this study was identical *to* that described by *Noah & Ceeracts* (11) (1971) in a *similar study* with *l* norepinephrine. Ten adult New Zealand rabbits and seventeen moderate to severe buphthalmic rab

bits of the same strain were used. Manometric decay curves were recorded with a Sanborn transducer and amplifying unit, two curves before and two curves after injection of ascorbic acid (Cevalin) into the anterior chamber. Approximately 4 mg and 12 mg were injected into the eyes of the normal and buphthalmic rabbits respectively. With this dosage the aqueous concentration was elevated by about fifty times normal. The difference in the quantity was in relation to the variation of total volume of aqueous in the normal and buphthalmic eye.

The induced manometric decay curves were evaluated by using the decay equation derived by *Noah & Geeraets* (11)

$$kC = \frac{1}{TP_s} \ln \frac{1-P_s/P_o}{1-P_s/P_T}$$

where k is the coefficient of ocular rigidity, C the facility of outflow, T the duration of the decay, P_s the steady state pressure, P_o the pressure at $t = 0$ and P_T the pressure at $t = T$. This equation gives a value for the product of the coefficient of ocular rigidity and the facility of outflow instead of solely the facility of outflow, this in order to eliminate unnecessary experimental error from separately determining the ocular rigidity by experimental means. The average decay values of the two pre-injection curves were compared with the average of the two post-injection curves.

Results

The mean kC products before and after administration intracamerally of the ascorbic acid are shown for normal and buphthalmic rabbit eyes in tables 1 and 2 respectively. A statistical analysis by the method of paired t testing is shown. The null hypothesis is established for a 5% significance level and gives the probability that ascorbic acid will not affect the kC product. The probability for accepting the null hypothesis is 0.005 for normal rabbits and 0.934 for buphthalmic rabbits. The significance therefore is great and the conclusion can be made that ascorbic acid raises the value of the kC product only in the normal rabbit eye. On the average this elevation was by about forty per cent.

Comments

The uncertainty of the relationship between ascorbic acid and the aqueous dynamics of the eye brings one to question the use of an equation that assumes a

Table 1

Results of the effect of asco bic acid on the kC product in normal rabb t eyes wit accompanying pa red t testing

Rabbit Number	Date of Experiment	$\overline{kC}$ (before drug)	$(\overline{kC})$ (after drug)	$\Delta kC = (\overline{kC}) - \overline{kC}$	Percent Change	$\Delta kC - \overline{\Delta kC}$	$(\Delta kC - \overline{\Delta kC})^2$
B 751 OS	8-01-69	0 0033	0 0035	0 00 ?	66 7	0 0000	0 0000×10⁻⁴
B- 0 OD	8-11 69	0 0055	0 0064	0 0009	16 4	0 0013	0 016?
B 763 OD	8-19-69	0 0064	0 0061	-0 0003	– 4 7	0 0075	0 0275
B-748-OD	8 25-69	0 0037	0 009?	0 0053	140 3	0 0031	0 0961
B-752 OS	9-08 69	0 0032	0 0051	0 0019	59 6	0 0003	0 0009
B 6 OD	9-15-69	0 0059	0 0091	0 003?	54 2	0 0010	0 0100
B 6 OS	9-2?-69	0 0040	0 0050	0 0010	25 0	0 0012	0 0144
B 67 OS	1?-08-69	0 0064	0 0065	0 0001	1 6	0 00 1	0 0441
B 5 OD	1?-15-69	0 0094	0 0138	0 0044	46 8	0 0022	0 0484
B- 59 OD	1-05-70	0 009	0 0127	0 003	33 7	0 0010	0 0100

$$\sum_{i}^{10} (\Delta kC)_i = 0\ 0719$$

$$\sum_{i}^{10} (\Delta kC - \overline{\Delta kC})^2_i = 0\ 0633 \times 10^{-4}$$

$$\overline{\Delta kC} = \frac{\sum_{i}^{n} (\Delta kC)_i}{n} = \frac{0\ 0719}{10} = 0\ 00??$$

$$s_{\Delta}kC = \sqrt{\frac{\sum_{i}^{n} (\Delta kC - \overline{\Delta kC})^2_i}{n-1}} = \sqrt{\frac{0\ 0633 \times 10^{-4}}{9}} = 0\ 0017$$

$$t_1 = t_3 = \frac{\overline{\Delta kC}}{s\ \overline{\Delta kC}/\sqrt{n}} = \frac{0\ 00??}{0\ 0017/\sqrt{10}} = 4\ 10$$

$P[\mu, \Delta kC = 0] \quad 0\ 005$ Reject the null hypothesis for the five percent significance level

Table 2

Results of the effect of ascorbic acid on the kC product in buphthalmic rabbit eyes with accompanying paired t testing

Rabbit Number	Date of Experiment	$\overline{kC}$ (before drug)	$(\overline{kC})$ (after drug)	$\Delta kC = (\overline{kC}) - \overline{kC}$	Percent Change	$\Delta kC - \overline{\Delta kC}$	$(\Delta kC - \overline{\Delta kC})^2$
28078-OS	7-28-69	0.0027	0.0027	0.0000	0.0	0.0006	0.0036 × 10^{-4}
73802-OD	8-18-69	0.0025	0.0049	0.0024	96.0	0.0030	0.0900
84448-OD	8-25-69	0.0014	0.0013	−0.0001	− 7.2	0.0005	0.0025
82081-OD	9-29-69	0.0038	0.0016	−0.0022	−58.0	0.0016	0.0256
82434-OD	9-30-69	0.0038	0.0025	−0.0013	−65.9	0.0007	0.0049
83906-OS	10-06-69	0.0047	0.0045	−0.0002	− 0.4	0.0001	0.0016
72711-OS	11-03-69	0.0039	0.0030	−0.0009	−23.0	0.0003	0.0009
83751-OD	11-10-69	0.0065	0.0054	−0.0011	−17.0	0.0005	0.0025
90188-OS	11-17-69	0.0023	0.0025	0.0002	8.7	0.0008	0.0064
81556-OS	11-24-69	0.0037	0.0029	−0.0008	−21.6	0.0002	0.0004
82327 OD	12-01-69	0.0059	0.0079	0.0020	33.9	0.0026	0.0676
73980-OS	1-12-70	0.0056	0.0028	−0.0028	−50.0	0.0022	0.0184
90188-OD	1-19-70	0.0071	0.0055	−0.0016	−22.6	0.0010	0.0100
90226-OD	1-26-70	0.0039	0.0021	−0.0018	−46.2	0.0012	0.0144
81740-OS	2-09-70	0.0047	0.0028	−0.0019	−40.4	0.0013	0.0169
74888-OD	2-23-70	0.0028	0.0029	0.0001	0.4	0.0007	0.0049

8 091 OS	3-0 70	0 0071	0 0038	-0 0013	-18 3	0 0007	0 0019
81556-OD	3-03 0	0 0010	0 0010	-0 0006	-37.5	0 0000	0 0000
90 76-OS	3 16-70	0 0017	0 0007	-0 0010	-58 9	0 0004	0 0016
3950-OD	3 23 70	0 0078	0 0031	0 0003	10 7	0 0009	0 0081
				$\sum_{1}^{20}(\Delta kC)_i = -0\ 0126$			$\sum_{1}^{20}(\Delta kC - \overline{\Delta kC})^2_i = 0\ 3052 \times 10^{-4}$

$$\overline{\Delta kC} = \frac{\sum_{1}^{n}(\Delta kC)_i}{n} = \frac{-0\ 0126}{20} = -0\ 0006 \qquad s_{\Delta kC} = \sqrt{\frac{\sum_{1}^{n}(\Delta kC - \overline{\Delta kC})^2_i}{n-1}} = \sqrt{\frac{0\ 3052 \times 10^{-4}}{19}} = 0\ 0013$$

$$t_{n-1} = t_{19} = \frac{\overline{\Delta kC}}{s_{\Delta kC}/\sqrt{n}} = \frac{-0\ 0006}{0\ 0013/\sqrt{19}} = -2\ 01$$

$P[\mu_{\Delta kC} = 0] = 0\ 934$ Accept the null hypothesis for the five percent significance level

constant rate of aqueous production It is felt by the authors that the kC products for post injection decay curves are valid only if sufficient time (usually from one half hour to one hour) has elapsed to allow the intraocular pressure to again attain steady state conditions although this base line pressure may differ from the P_s recorded prior to the injection of the ascorbic acid into the anterior chamber A reasonable constancy of the rate of aqueous production is assumed during the recording of the decay curve

An increase in the ocular rigidity by ascorbic acid as suggested by *Linner* (6), would appear to be rather remote Indeed in his later works he apparently reversed his earlier premise In this study the authors feel justified in assuming that no significant variation in the ocular rigidity occurs with the administration of ascorbic acid Then any fluctuation in the kC product reflects change essentially in the facility of outflow

In both normal and buphthalmic rabbits it was noted that immediately following injection of ascorbic acid into the anterior chamber the steady state pressure P_s usually demonstrated a gradual rise After twenty to fifty minutes in normal rabbits however it tended to fall back to its original level In the buphthalmic rabbits a return to its previous value was usually incomplete It is our feeling that this phenomenon is either due to a marked osmotic shift of fluid from the plasma to the aqueous humor or due to the increase in viscosity of the aqueous caused by the ascorbic acid or perhaps to a combination of the two Indeed the phenomenon is a curious one for in the buphthalmic eyes the probability of 0 934 of accepting the null hypothesis strongly suggests that ascorbic acid in these eyes actually decreases the facility of outflow at least during our time of observation

Summary

This study confirms other investigations by demonstrating that ascorbic acid does influence the aqueous dynamics of the normal eye It was shown in this work that it probably increases the facility of outflow in the normal adult rabbit eye although other mechanisms cannot be ruled out The fact that the buphthalmic eye of congenital glaucoma did not respond to this compound indicates that perhaps as has been suggested by other investigators pathologic mucopolysaccharides do exist in the angles of these eyes or that there is present an essentially functionless trabeculum

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From the Coagulation Laboratory (Director Prof I M Nilsson) and from the Eye Clinic (Director Prof G Östlind) Malmö General Hospital University of Lund Malmö Sweden

ONTOGENESIS OF A FIBRINOLYTIC ACTIVATOR IN THE HUMAN EYE

BY

MAURIZIO PANDOLFI and BIRGER ASTEDT

It is generally accepted that the function of the blood fibrinolytic system is to maintain fluidity of the circulating blood and to dissolve any obstructing thrombi (*Astrup* 1956 *Sharp* 1969) Cumulative evidence suggests that the fibrinolytic agents in the blood derive from the endothelium of certain vessels especially small vessels which contain large amounts of an activator of fibrinolysis tissue plasminogen activator (Nilsson & Pandolfi in press) Tissue plasminogen activator catalyses the conversion of plasminogen a plasma globulin into plasmin a proteolytic agent capable of dissolving fibrin According to *Ekelund et al* (1970) fibrinolytic activity is present in foetal blood already in the 12th week of gestation its function then being to maintain the patency of the foeto maternal circulation

The development of fibrinolytic activity has recently been studied in the tissues of the rat s eye (*Pandolfi* 1967) The present investigation deals with the microscopical localization of tissue plasminogen activator in the human foetal eye

This investigation was supported by grants from the Swedish Medical Research Council (B70-19X 87-06C)

Received December 16th 1970

Material and Methods

The material consisted of 53 eyes from 41 eight to twenty six week old embryos and foetuses (Table I). The mothers were healthy and their pregnancies were *terminated on socio medical grounds*. The uterus was emptied by abdominal hysterotomy under general anaesthesia with $O_2 + N_2O$ and fluothane. As a rule the eyes were carefully enucleated immediately after the extraction of the foetus and quickly frozen with rapidly expanding CO_2. If the foetus was in an early stage of development (14 weeks of gestation or before) the entire head was frozen. The eyes or the heads were transferred to a cryostat microtome and cut into 6 to 8 μm thick sections.

The localization of tissue plasminogen activator in the eye was studied by a modification of *Todd's* (1959) fibrin slide technique. The frozen sections were collected on microscope slides and then covered with a mixture of 60 μl of a fibrinogen solution prepared essentially according to *Brakman* (1967) (1 % plasminogen rich bovine fibrinogen in phosphate buffer pH 7.8 final ionic

Table I
Distribution of the material

Week of Pregnancy	Number of foetuses
8	2
10	1
10–11	1
11	2
12	2
13	2
14	1
14–15	1
15–16	1
16	3
17	4
18	3
19–20	1
20	4
21	4
23	2
24	5
26	2
Total number	41

From the Coagulation Laboratory (Director Prof. I. M. Nilsson) and from the Eye Clinic (Director Prof. G. Östcrlind) Malmö General Hospital, University of Lund, Malmö, Sweden

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BY

MAURIZIO PANDOLFI and BIRGER ÅSTEDT

It is generally accepted that the function of the blood fibrinolytic system is to maintain fluidity of the circulating blood and to dissolve any obstructing thrombi (*Astrup* 1956, *Sharp* 1969). Cumulative evidence suggests that the fibrinolytic agents in the blood derive from the endothelium of certain vessels, especially small vessels which contain large amounts of an activator of fibrinolysis, tissue plasminogen activator (Nilsson & Pandolfi in press). Tissue plasminogen activator catalyses the conversion of plasminogen, a plasma globulin, into plasmin, a proteolytic agent capable of dissolving fibrin. According to *Eklund et al.* (1970), fibrinolytic activity is present in foetal blood already in the 12th week of gestation, its function then being to maintain the patency of the foeto-maternal circulation.

The development of fibrinolytic activity has recently been studied in the tissues of the rat's eye (*Pandolfi* 1967). The present investigation deals with the microscopical localization of tissue plasminogen activator in the human foetal eye.

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of the primary neuro epithelium into inner and outer neuroblastic layer has just passed the equator *Fibrinolysis is demonstrable only in the apices of the orbits*

In the 14th week lysis begins to appear at the junction between the optic nerve and the walls of the eye Later areas of fibrinolysis can be seen at the sites of angioblastic cells of the developing choroid (Fig 2) Thereafter the

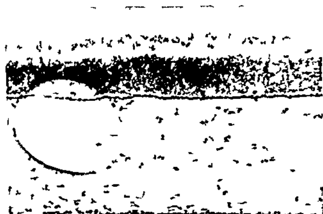


Fig 2
Posterior wall of the eye of a 16 week old foetus Ganglion cell layer distinctly separated from inner neuroblastic layer Two circular areas of fibrinolysis of different size confined to cells of developing choroid Incubation time 60 minutes (X 30)

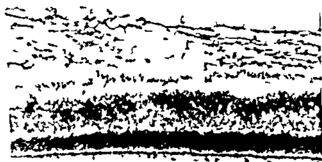


Fig 3
Retina in proximity of the papilla in a 24 week old foetus *Inner nuclear layer now* clearly separated from nuclei of rods and cones Single faint area of lysis confined to fiber layer Incubation time 60 minutes (X 30)

strength 0 15) and of 10 μl of thrombin solution (Topostasine® 20 NIH units/ml of unbuffered saline) spread over an area of 10 cm² to form a 40 μm thick fibrin film After incubation in a moist chamber (37°C) for 15 30 45 and 60 minutes the slides were fixed in 10 % formaldehyde solution (formalin) and stained with Harris alum hematoxylin During the incubation plasminogen activator liberated by the active cells of the section transforms fibrin s plasminogen into plasmin with consequent local dissolution of the fibrin film. The presence of fibrinolytic activity (plasminogen activator activity) is reflected by clear zones of lysis at the sites of the active cells Different tissues were compared regarding the strength of their fibrinolytic activity as estimated from the minimum incubation time necessary for producing fibrinolysis and from the size of the areas of lysis

Results

No fibrinolytically active cells could be demonstrated in the developing eye before the 14th week of gestational age Fig 1 shows a transverse section of the head of a 10 week old foetus The section passes through both eyes Medially to the left eye are the developing nasal bones with the septum to the right the posterior-medial wall of the right eye Behind, the medial cranial fossa with the anterior part of the diencephalon As shown by the left eye, differentiation

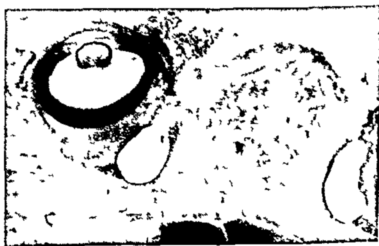


Fig 1
Transverse section of the head of 10 week old foetus Section passing through the eyes (× 5) For explanation see text



Fig 5

Cross section of optic nerve from [illegible]6 week old foetus Lysis present at the central retinal artery and vein (arrow) and, in a higher degree at the sites of surrounding meningeal sheets Incubation time 30 minutes ($\times 12^{1}/_{2}$)

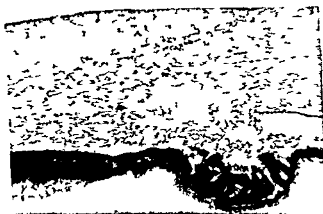


Fig 6

Corneoscleral junction in a [illegible]0 week old foetus Note the cleft between the primordia of the trabeculae and the tissue of the iris and ciliary body The section illustrates the passage of the pigmentary and nervous part of the retina into pigmented and unpigmented ciliary epithelium respectively Fibrinolysis is solely at the site of the developing canal of Schlemm and deep scleral plexus Incubation time 45 minutes ($\times 17^{1}/_{2}$)

and physiological requirements vary rapidly and this is reflected in equally rapid changes of tissue enzymatic features. Our scanty knowledge of development physiology makes it difficult to predict and explain the appearance and

choroid increases in activity The retina is essentially inactive until the 22-23rd week, when faint areas of fibrinolysis begin to appear sporadically in the fiber layer (Fig 3) The outer part of the sclera begins to show sites of activity after the 16–17th week at the entrance of blood vessels The dura and the central retinal vessels inside the optic nerve show fibrinolytic properties as soon as they are histologically recognizable (Fig 4 and 5)

After the 16–17th week fibrinolysis appears at the corneoscleral junction The activity of this structure is initially low (Fig 6) but it soon increases causing large areas of lysis sometimes involving the entire chamber angle (Fig 7) As shown by Fig 6 lysis appears at the site of the future canal of Schlemm present at this stage of development (20 weeks) as a thin walled venous plexus, and of the deep scleral vascular plexus The cornea the iris and ciliary body and the lens were inactive throughout the period of development studied. Neither in the space occupied by the primary vitreous body was fibrinolysis demonstrable

Comments

In fully differentiated organisms owing to the established pattern of growth and function the distribution of the enzymes in tissues and their local ratios tend to remain constant But in developing organisms anatomical relationships



Fig 4

Posterior wall of eye of 25 week old foetus at the junction with the optic nerve High fibrinolytic activity at the dura surrounding optic nerve and at the bulb of hyaloid artery (arrow) Minor zones of lysis at choroid and at sclera Incubation time 45 minutes (× 7½)

bryonic life but no activity is *demonstrated in the choroid* before the 16th week. The fibrinolytic activity in the iris and retina in the fully differentiated eye is high (*Pandolfi* 1967a *Pandolfi & Kwaan 1967*) *Since these structures are barely* active before up to the 26th week i e. after their vascularization one must assume that their vessels acquire fibrinolytic properties between the 26th week stage and birth It is possible that the beginning of certain functions in a tissue stimulates the expression of the gene regulating the synthesis of tissue plasminogen activator a phenomenon known as enzymatic induction. This condition apparently never occurs during the life of other vessels such as ciliary body vessels (*Pandolfi & Kwaan* 1967) placental vessels (*Beller et al* 1962) and liver sinusoid (*Todd* 1959)

Also the hyaloid vascular system in its intravitreal course and the tunica vasculosa lentis are never active in the human in contrast with the rat where *this system is very active (Pandolfi 1967)* But *these two* vascular systems are not strictly comparable in the rat these vessels reach their highest state of development at birth (*Ashton 1968*) while in man *they begin to atrophy already* at the 60 mm stage (*Duke Elder* 1963)

The relatively early appearance as well as the intensity of fibrinolytic activity at the site of the vessels involved in the drainage of the aqueous humor is noteworthy Since the appearance of tissue plasminogen activator is a sign of cellular differentiation and function the fibrinolytic activity of the chamber angle may suggest circulation of aqueous humor in the foetal eye.

Summary

The occurrence of a fibrinolytic enzyme tissue activator of plasminogen was studied *in the developing human eye. No fibrinolytically* active cells could be demonstrated until the 14th week of gestational age when fibrinolysis began to occur at the *junction of the optic nerve* with the ocular walls Later fibrinolytic activity began at the sites of angioblastic cells of the choroid and later on in the 22-23rd week a faint fibrinolytic activity confined to the retina was sometimes observed An increasingly high fibrinolytic activity was present at the *corneoscleral* junction after the 16-17th week Other structures active in the differentiated human eye e g the iris and in the developing eye of rat e g the *hyaloid vascular system* did not show any activity during the period examined Tissue plasminogen activator presumably serves to maintain the patency of the foetal circulation and its appearance in a developing tissue may be taken as a sign of differentiation



Fig 7
Low power view of the anterior chamber s angle in 26 week old foetus Both sections show a large lytic area covering the entire corneoscleral junction Minor foci of fibrino lysis produced by episcleral vessels Incubation time 60 minutes (X 5)

the quantitative changes of an enzyme occurring at a given stage of develop ment (*Kretchmer et al* 1963) Generally, during the early embryonal life enzymes concerned with the maintenance and growth of tissue prevail with the progress of the differentiation these enzymes are balanced by other enzymes involved in various cellular functions (*Richter* 1961) Tissue plasminogen acti vator clearly belongs to the second class of enzymes and its presence in a de veloping tissue may therefore be taken as a sign of differentiation

In the period of development studied three structures become clearly active viz the sclera at the intramural course of ciliary vessels the choroid and the corneoscleral junction The other structures remained essentially inactive not only the cornea lens and ciliary body which are inactive also in the fully differentiated eye (*Pandolfi* & *Kwaan* 1967) but also the iris and the retina which are very active after birth (*Pandolfi* 1967*a* *Pandolfi* & *Kwaan* 1967)

The reasons for the appearance of plasminogen activator in ocular tissues and for the absence of the enzyme up to the 26th week of development in structures known to be active after birth are obscure Tissue plasminogen activator is known to be contained in the walls of blood vessels These results show that the anatomic appearance of vessels in a tissue does not necessarily imply the oc currence of fibrinolytic activity in that tissue This is well illustrated by the fibrinolytic activity of the choroid As known (*Duke Elder* 1963) choroidal vessels cover the outer layer of the optic cup as early as the 6th week of em

bryonic life but no activity is demonstrated *in the choroid before the 16th week* The fibrinolytic activity in the iris and retina *in the fully differentiated eye is* high (*Pandolfi* 1967a *Pandolfi* & *Kwaan* 1967) *Since these structures are barely* active before up to the 26th week i e after their vascularization *one must* assume that their vessels acquire fibrinolytic properties between the 26th week stage and birth It is possible that the beginning of certain functions in a tissue stimulates the expression of the gene regulating the synthesis of tissue plasminogen activator a phenomenon known as enzymatic induction This condition apparently never occurs during the life of other vessels such as ciliary body vessels (*Pandolfi* & *Kwaan* 1967) placental vessels (*Beller et al* 1962) and liver sinusoid (*Todd* 1959)

Also the hyaloid vascular system in its intravitreal course and the tunica vasculosa lentis are never active in the human in contrast with the rat where this system is very active (*Pandolfi* 1967) But these two vascular systems are *not strictly* comparable in the rat these vessels reach their highest state of *development* at birth (*Ashton* 1968) while in man they begin to atrophy already at the 60 *mm stage* (*Duke Elder* 1963)

The relatively early appearance as well as the intensity of fibrinolytic activity at the site of the *vessels involved* in the drainage of the aqueous humor is noteworthy Since the *appearance of tissue* plasminogen activator is a sign of cellular differentiation and *function the fibrinolytic* activity of the chamber angle may suggest circulation of aqueous humor in the foetal eye

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From the University of Bergen School of Medicine Department of Ophthalmology (Head Professor Torstein I Bertelsen M D)

THE SAGITTAL GROWTH OF THE EYE

II Ultrasonic measurement of the axial diameter of the lens and the anterior segment from birth to puberty

BY

JON S LARSEN

We have only an incomplete knowledge of the axial diameter of the lens and of the growth rate of the anterior segment during the postnatal growth period With regard to the growth rate of the anterior segment measurement of the distance from the vertex of the cornea to the posterior pole of the lens may give valuable information

The object of this work is to study the development of the thickness of the lens from birth to puberty and to throw light upon the growth of the anterior segment

In 1883 Smith showed that the lens increases in weight throughout life the increase from the age of 20 to the age of 80 being approx 100 mg According to Scammon & Hesdorffer (1937) the weight of the lens in newborns is approx 65 mg increasing to about 1?4 mg towards the end of the first year of life The weight of the lens then increases slowly throughout life reaching a weight of approx 2?8 mg at the age of 80–90 years Johansen (1947) reported largely similar findings In adults this factor is reflected in the increasing thickness of the lens with increasing age (Saunte 190? Zeeman 1911 Raeder 1922) As it will appear from Table 1 post mortem studies have also shown a great variation in the thickness of the lens in newborns with values from 3 ? to 5 mm

Since 1961 a large number of papers have been published on biometric measurements of the eye made by ultrasound The thickness of the lens is a factor

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Table 2

Earlier determinations of the lens thickness *in vivo* M = males F = females

Author	Age	Thickness of lens mm (mean) M	F	No of eyes M	F
	days				
Gernet (1964)	1– 5	3 4	3 4	41	29
Luyckx (1966)	4– [illegible]	3 7 (3 4–4 1)	3 6 (3 4–4 1)	54	50
	years				
Gernet & Hollwich (1968)	0– 2	3 87		15	
Gernet & Hollwich (1968)	0–1[illegible]	3 81		66	
Sorsby et al (1963)	7–10	3 54	3 57	7	10
Sorsby et al (1963)	11–13	3 45	3 55	11	13
Raeder (19[illegible])	9–13	3 89		8	
Saunte (190[illegible])	10–19	3 6[illegible]			
	20–[illegible]9	3 68			
	30–39	3 99		98	
	40–49	4 29			
	58–67	4.5[illegible]			
Zeeman (1911)	1[illegible]–30	3 6[illegible]		25	Hypermetropia
		3 [illegible]0		25	Emmetropia
		3.54		25	Myopia
Jansson (1963)	15–19	3 478	3 479	29	9
	[illegible]0–[illegible]9	3 614	3 668	54	[illegible]7
	30–39	3 [illegible]84	4 005	18	13
	40–49	4 189	4 098	8	17

Ultrasonographic measurements

Salminen (1968) using an echo threshold moved by a potentiometer found a measurement error of approximately 0 1–0 2 mm

Table 1
Measurements of lens thickness *in vitro*

Author	Age	Thickness of lens mm (mean)	No of eyes
von Jaeger (1861)	Newborns	4 5	10
Merkel & Orr (1892)	Newborns	5 0	?
Collins (1894)	Newborns	4 3	3
Heine (1898)	Newborns	3 5	1
Stadfeldt (1898)	Newborns	3 93	11
von Pflugk (1911)	Newborns	3 76	7
	Months		
	9–12	2 46	
	Years		
	1–2	2 57	
Dub (1891)	2–3	2 72	33
	3–4	2 83	
	4–5	3 0	
	5–6	3 2	
	7	2 9	
	12	3 6	

in the calculation of the axial length of the eye Using this method Gernet (1964) arrived at an average thickness of the lens in newborns of 3 4 mm whereas Luyckx (1966) found values of 3 6–3 7 mm Gernet & Hollwich (1968) appear to be the only workers who have carried out biometric measurements *in vivo* during the growth period from birth to puberty (66 emmetropic eyes) although the only values given for the thickness of the lens are the mean values for the age groups 0–2 years and 0–12 years respectively 3 87 and 3 81 mm In older children (7–13 years) Sorsby et al (1963) found values of approx 3 5 mm using ultrasonic measurement whereas Raeder s material (1922) gives a mean value of 3 89 mm Table 2 presents a survey of the results of earlier lens measurements *in vivo* for the growth period

In 1963 Jansson gave the error of the method in ultrasonographic measurement of the axial diameter of the lens as 0 045 3 SD = ± 0 135 mm Sorsby et al (1963) made comparative measurements by using ultrasonography and phacometry Examinations of 140 eyes gave a mean difference of + 0 099 ± 0 20 mm in measurements of the thickness of the lens

In ultrasonic measurements of axial diameter in pig s lenses Oksala &

Table 3 (cont)

Age years								
5–6	6–7	7–8	8–9	9–10	10–11	11–12	12–13	13–14
							2	
			2				2	
			4	4	2		2	
	1	1	8	6	10	2	2	4
	3	7	6	12	12	8	10	2
10	26	11	20	12	10	16	20	16
16	17	24	24	18	14	14	8	2
26	11	14	16	16	4	6	6	
5	2	9	12	8		2	4	
3	4			4		4		
4		2	4		4			
		2	4					
64	64	70	100	80	56	52	56	24
3 60	3 49	3.54	3 48	3 47	3 40	3 47	3 38	3 36
0 09	0 14	0 18	0 14	0 20	0 2[illegible]	0 17	0 21	0 12
0 011	0 018	0 022	0 014	0 022	0 029	0 0[illegible]4	0 0 8	0 0[illegible]4

anisometropia greater than 2 D being excluded from the examination. With the exception of the newborns the examination was made under cycloplegia induced by Cyclogyl® both eyes being examined in all subjects

The apparatus used was a Siemens Echo ophthalograph (System Krautkramer) type USIP 10 and a 6 Mc/5 mm transducer The echogram was photographed from the oscilloscope screen by a polaroid camera the thickness of the lens being measured from the photograph to an accuracy of 0 1 mm The velocity of ultrasound in lens tissue at 37°C is approx 1641 m/sec (Jansson

Table 3

Lens thickness in the present male series SD standard deviation SE standard error

Thickness of lens mm	Days 1–5	Months 6	Months 9	Age years 1–2	2–3	3–4	4–5
2 80–3 89							
2 90–2 99							
3 00–3 09					1		
3 10–3 19							
3 20–3 29							3
3 30–3 39				2	12	13	19
3 40–3 49				15	36	31	29
3 50–3 59	5			4	32	36	22
3 60–3 69	7			11	19	17	20
3 70–3 79	10			2	10	1	7
3 80–3 89	12	2	2		5	7	6
3 90–3 99	14						
4 00–4 09	18				3	5	1
4 10–4 19	6						
4 20–4 29	8			1			
4 30–4 39	4			1			
4 40–4 49	2		2				
Number of eyes	86	2	4	36	118	110	100
Mean	3 93	3 89	4 17	3 64	3 62	3 62	3 61
SD	0 17	–	–	0 21	0 20	0 25	0 17
SE	0 018	–	–	0 035	0 018	0 024	0 017

Material and method

The material examined and the method used have been described in detail in an earlier paper (Larsen 1971a) Only the main features will be given here The examination comprises 80 mature newborns 43 boys and 37 girls In the age group 6 months–13 years 465 boys and 381 girls with healthy eyes were examined those in the age group 6 months 7 years under general anaesthesia All of these eyes had refraction values between + 5 D and – 5 D those with

Table 4 (cont)

Age years								
5–6	6–7	7–8	8–9	9–10	10–11	11–12	12–13	13–14
								4
			4		4		2	8
	3	6	4	2	6		4	2
9	15	16	4	20	10	40	24	8
9	14	19	10	12	10	24	22	10
11	24	7	6	10	10	2	10	12
11	4	2	4	4	2	2	4	
	2						4	
6	2				2	2	6	4
						2		
46	64	50	32	48	44	72	76	48
3 62	3 55	3 46	3 47	3 49	3 47	3 48	3 52	3 45
0 14	0 14	0 11	0 18	0 11	0 19	0 15	0 18	0 25
0 021	0 008	0 016	0 032	0 016	0 029	0 018	0 021	0 036

sults can be compared To provide a broader basis of comparison measurements were made of the right eye of 10 emmetropic men and 10 emmetropic women in the age group 20–40 years

It is not known whether the accommodation paralysis induced by medication in newborns has any influence on the thickness of the lens In order to investigate this question the right eye of 3 newborns was measured before and from one half to one hour after application of cyclopentolate hydrochloride 1 % and metaoxidrine 2 % eye drops.

Table 4

Lens thickness in the present female series SD standard deviation SE standard error

Thickness of lens mm	Days 1–5	Months 6	Months 9	Age years 1–2	2–3	3–4	4–5
3 00–3 09							
3 10–3 19							
3 20–3 29					1		
3 30–3 39				2	11	12	6
3 40–3 49	1			5	24	18	99
3 50–3 59	5			6	25	24	15
3 60–3 69	4			5	25	21	13
3 70–3 79	8		2		10	9	9
3 80–3 89	10	2		2	4	6	1
3 90–3 99	6						
4 00–4 09	15			2	1		
4 10–4 19	6						
4 20–4 29	13				1		
4 30–4 39	4						
4 40 4 49	2						
4 50–4 59					2		
Number of eyes	74	2	2	22	104	90	66
Mean	3 99	3 89	3 78	3 67	3 65	3 64	3 58
SD	0 23	–	–	0 19	0 20	0 15	0 12
SE	0 027	–	–	0 041	0 020	0 016	0 015

1963) *The oscilloscope scale showed full linearity below 18 mm* the thickness of the lens being computed by multiplying the echo reading by the factor k = 1 1 in which k is determined by the principle earlier described (Larsen 1971a)

In order to determine the degree of accuracy of the results of measurements 10 different measurements were made of the right eye of an adult subject The results of these investigations gave the mean value 3 65 mm SD = 0 066 3 SD = 0 199

There are few measurements from the post natal period with which the re

Table 5

Lens thickness and length of anterior segment (mean values) in hypermetropic emmetropic and myopic boys and girls for the age groups 1–3 years and for 12 year old girls A depth of anterior chamber B thickness of lens A + B length of anterior segment (corneal vertex – posterior pole of lens) M = males F = females

Distances	Age in years								
	1–3						12		
	Hypermetropia		Emmetropia		Myopia		H	E	M
	M	F	M	F	M	F	Females		
Depth of chamber (A) mm (mean)	3 36	3 31	3 50	3 37	3 64	3 47	3 33	3 60	3 88
Thickness of lens (B) mm (mean)	3 63	3 65	3 63	3 65	3 63	3 66	3 47	3 62	3 47
A + B	6 99	6 96	7 13	7 02	7 27	7 13	6 80	7 22	7 35
No of eyes	158	107	86	106	20	8	28	28	20

Results

Tables 3 and 4 show the thickness of the lens in the different age groups for boys and girls respectively, refraction not being taken into account As it appears from the tables there is a wide range in thickness of the lens in all year classes Except for the newborns measurements of the lens thickness were made under cycloplegia induced by cyclopentolate hydrochloride 1 % (Cyclogyl®)

Distributed by age groups, the mean values found were as follows

	1–5 days	1–3 yrs	4–7 yrs	8–10 yrs	11–13 yrs
Boys	3 93 mm	3 63 mm	3 56 mm	3 45 mm	3 41 mm
Girls	3 99 mm	3 65 mm	3 55 mm	3 48 mm	3 49 mm

The question of whether refraction affects the thickness of the lens during the growth period was investigated in both sexes for age groups 1 2 and 3 years, and for 12 year old girls

It was only in these classes that the refraction range was of such magnitude that adequate results might be expected (tabular values of refraction were given in an earlier work Larsen 1971a Tables 4 and 5) As it appears from Table 5 no relation was found between the thickness of the lens and refraction neither in the age group 1–3 years nor in 12 year old girls Such a relationship does not appear to be present in adults either although the lens is often rather thinner in myopia than in other refraction forms (Zeeman 1911 Raeder 1922)

It has long been known that the lens thickness in older children and adults increases on accommodation the depth of the anterior chamber simultaneously decreasing (Helmholtz 1855 Heine 1898 Saunte 1905 Zeeman 1911 Karpe 1938) Calmettes et al (1958) found on examining two 8 year old boys that at maximum accommodation the depth of the anterior chamber decreased 0 38 mm and 0 20 mm respectively compared with measurements made under cycloplegia

In this investigation no significant difference could be demonstrated in the thickness of the lens in newborns between measurements made without or under cycloplegia The results must be considered with reservations as the conditions of examination are far from optimum in repeated examinations of newborns due to increasing restlessness Five measurements were made of the same eye both without (I) and under cycloplegia (II) the following mean values were found

	I mm	II mm
1	4 22	4 22
2	3 89	3 85
3	4 00	3 96

Table 7

Lens thickness and length of anterior segment (corneal vertex – posterior pole of lens) in year classes A depth of anterior chamber B thickness of lens A + B length of anterior segment.

Age	Boys A	Boys B	Boys A+B	Boys Range		Girls A	Girls B	Girls A+B	Girls Range	
Days 1–3	2.37	3.93	6.30	5.80	6.90	2.39	3.99	6.38	5.80	7.10
Years 1–2	3.55	3.64	6.99	6.57	7.42	3.24	3.67	6.91	6.57	7.12
2–3	3.38	3.62	7.00	6.57	7.12	3.35	3.65	7.00	6.57	7.67
3–4	3.50	3.62	7.12	6.57	7.44	3.35	3.64	6.99	6.57	7.67
4–5	3.52	3.61	7.13	6.68	7.74	3.37	3.58	6.95	6.59	7.44
5–6	3.52	3.60	7.12	6.47	7.44	3.39	3.67	7.01	6.57	7.66
6–7	3.54	3.49	7.03	6.59	7.75	3.44	3.55	6.99	6.57	7.53
7–8	3.61	3.54	7.15	6.79	7.53	3.59	3.46	7.05	6.68	7.44
8–9	3.63	3.48	11	6.45	7.65	3.60	3.47	7.07	6.57	7.63
9–10	3.63	3.47	7.10	6.57	7.44	3.56	3.49	7.05	6.68	7.42
10–11	3.66	3.40	7.06	6.57	7.65	3.59	3.47	7.06	6.35	7.65
11–12	3.64	3.47	7.11	6.[illegible]8	7.44	3.63	3.48	7.11	6.68	8.10
12–13	3.71	3.38	7.09	6.34	7.54	3.57	3.5[illegible]	7.09	6.[illegible]9	7.46
13–14	3.[illegible]0	3.36	7.06	6.78	7.4[illegible]	3.62	3.45	7.07	6.55	7.42

age of 8–10 when the flattening out process appears to have stopped or almost stopped Earlier investigations appear to show that the lens is almost spherical at birth (Merkel & Orr 1892) Measuring the radii of curvature of the lens of an 11 day old child Holth (1899) found values of 4 5 and 4 1 mm for the anterior surface of the lens 4 0 and 3 85 for the posterior surface In a 21 month old child the values were 6 39 and 4 1 mm respectively Von Pflugk (1909) measured the radii of curvature of 7 lenses in newborns and found mean values of 5 mm for the anterior surface 4 mm for the posterior surface The spherical form of the lens appears to be the explanation of the relatively great anterior posterior diameter in this age group

If the results of this work with regard to the thickness of the lens are compared with earlier studies made in newborns in vitro it will be seen that they accord well with the values found by Stadfeldt (1898) and von Pflugk (1911) but are smaller than the values reported by von Jaeger (1861) and Merkel & Orr (1892) (cf Table 1) Cernet (1964) and Luyckx (1966) on the other hand found lower values on in vivo measurements than those in the present study

In the case of emmetropic adults (age 20–40 years) the results of measurements showed a mean value for lens thickness of 3 82 mm in men and 3 70 in women These findings are in good accord with values from earlier studies (Saunte 1905 Zeeman 1911 Jansson 1963 cf Table 2)

The growth of the anterior segment illustrated by the distance from the corneal vertex to the posterior pole of the lens is given in Table 6 for all year classes

The following mean values were found

	1–5 days	1–3 yrs	4–7 yrs	8–10 yrs	11–13 yrs
Boys	6 30 mm	7 08 mm	7 11 mm	7 09 mm	7 09 mm
Girls	6 38 mm	6 99 mm	6 99 mm	7 06 mm	7 09 mm

In an earlier work (Larsen 1971a) a relation was found between refraction and the depth of the anterior chamber in the growth period the anterior chamber being deepest in myopes and shallowest in hypermetropes A similar relationship shown in Table 5, is also present between the length of the anterior segment (corneal vertex pole of posterior lens) and the different forms of refraction

Discussion

In this study the mean value for the thickness of the lens was found to decrease by approx 0 3 in the first year of life and then by approx 0 2 mm until the

Table 6
Percentage distribution of lens thickness in the present material
M = males F = females

Thickness of lens mm	Age									
	Days 1–5		Years 1–3		4–7		8–10		11–13	
	M	F	M	F	M	F	M	F	M	F
≤ 3 39	0	0	10 6	12 0	24 8	24 3	45 7	43 5	65 2	46 9
3 40–3 79	25 6	23 7	81 1	79 6	70 1	71 7	48 3	54 8	34 8	45 9
3 80–4 19	58 1	48 7	7 6	6 9	5 0	4 0	5 1	1 6	0	7 1
≥ 4 20	16 3	25 0	0 7	1 4	0	0	0	0	0	0
No of eyes	86	76	264	216	298	226	236	124	132	196

depth of the anterior chamber it appears as if the distance between the corneal vertex and the posterior pole of the lens reflects the magnitude of the corneo scleral segment for the different forms of refraction in the period of growth it being greatest in myopes and smallest in hypermetropes The anterior segment appears to grow very little after the age of 2–3 years and the increases in the length of the eye after this time must depend mainly on an increase in the length of the posterior segment This question will be further elucidated in a later work

Summary

The axial diameter of the lens and the length of the anterior segment (from the corneal vertex to the posterior pole of the lens) were measured by ultrasonography in 80 mature newborns (43 boys and 37 girls) and in 465 boys and 381 girls aged 6 months to 13 years Both eyes were measured in all individuals No significant difference was found between the thickness of the lens in the two sexes during the period of growth

In newborns the mean value of the axial diameter of the lens was 3 93 mm in boys 3 99 mm in girls During the first year and a half of life the thickness of the lens decreased by approx. 0 3–0 4 mm in both sexes with a further reduction of approx 0 2-0 3 mm by puberty (11–13 years)

In newborns the length of the anterior segment was approx 6.3–6 4 mm the increase by the second year of life being approx 0 7 mm in boys approx 0.5 mm in girls The longitudinal growth of the anterior segment after the second year of life was only approx 0 1 mm the increase in the length of the eye after this age appearing to depend mainly upon an increase in the length of the posterior segment of the eye

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However as these authors made their examinations under cycloplegia the values are not directly comparable although no significant difference in the thickness of the lens measured without and under cycloplegia was established in the present study

In the case of older children there is good accord between the results in this study and the values given by Sorsby et al (1963) The values found for older children are however, smaller than those reported by Raeder (1922), but his values for adults are higher than those given by most authors (cf Table 2)

Gernet & Hollwich (1968) appear to be the only investigators who give the values of the axial diameter of the lens during the period of growth from birth to the age of 12 These results are however given as mean values for the age group 0–2 years (15 eyes) and for the whole period of growth from 0–12 years with values of 3 87 ± 0 241 mm and 3 81 ± 0 643 mm respectively For small children (0–2 years) there is good agreement between the results of measurements in the present work and the values reported by these authors In the case of older children the values are difficult to compare The mean value given by Gernet & Hollwich however is somewhat higher than those found in this study where less than 8 per cent of the lenses measured after the age of one year had values above 3 80 mm (Table 6) The difference in the results is not great and may perhaps result from the material used by the authors mentioned being relatively small (66 emmetropic eyes) and having a considerable physiological range in the axial diameter of the lens

In the present study the thickness of the lens in girls was found in each group to be a little greater than in boys The difference is less than 0 09 mm in all age groups and may thus be an expression of the error of the method This difference can therefore not be considered as real No correlation was found between refraction and lens diameter during the growth period or between the thickness of the lens and the depth of the anterior chamber

The growth in the length of the anterior segment (corneal vertex – posterior pole of lens) from birth to the second year of life amounts to approx 0 7 mm in boys and 0 5 mm in girls After the age of 2–3 years however the growth in the length of the anterior segment appears to stagnate (Table 7) the length of the anterior segment increasing by less than 0 1 mm after this age After the age of 5 the increase in the depth of the anterior chamber appears to be caused mainly by a flattening out of the anterior surface of the lens From this age the depth of the anterior chamber increases in both sexes by about 0 2 mm until puberty the lens being flattened out to about the same extent This factor is reflected in the finding that the length of the anterior segment is fairly constant after early childhood The growth rate of the cornea which appears to reach full size before the age of 5 years (Smith 1890 Peter 1924 Kaiser 1962) is of importance in this connection

As no correlation has been found between the thickness of the lens and the

From the University of Bergen School of Medicine
Department of Ophthalmology
(Head Professor Torstein I Bertelsen M D)

THE SAGITTAL GROWTH OF THE EYE

III Ultrasonic measurement of the posterior segment (axial length of the vitreous) *from birth to puberty*

BY

JON S LARSEN

Measurement of the posterior segment (posterior pole of the lens – posterior wall of the eye) is a necessary part of the ultrasonic determination of the optic axis

In newborns the mean values for the length of the posterior segment appear to be of the magnitude of 10–11 mm. In Gernet s material (1964) the mean values in newborn boys were given as 10 8 mm in newborn girls as 10 9 mm Luyckx (1966) found values from 9 7–11 5 mm in newborn boys 10 1–11 6 mm in girls

Gernet & Hollwich (1968) made ultrasonic measurements of the vitreous during the post natal growth period from 0–12 years in 66 emmetropic eyes They found that the length of the vitreous increased asymptotically with a rapid longitudinal growth during the first year of life Mean values of approx 14 mm were found at the age of 1 year and values of approx 15 mm at 3 years Subsequently there was a slow and gradual increase to approx 15 5 mm at the age of 12 As far as it can be seen from the literature Gernet & Hollwich are the only workers who have made biometric measurements of the length of the vitreous in the growth period from birth to the age of 12

For adults in the age groups 15–49 years 177 eyes with various ocular refraction Jansson (1963) reports values between 15 64 and 16 8 mm Gernet (1964)

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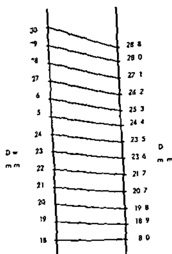


Fig 1
Nomogram for calculation of vitreous Dw = Water column
Do = Oscilloscope scale.

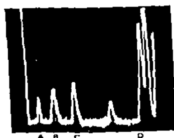


Fig 9
Echogram from a 56 year old man with amotio retinae. A) Anterior corneal surface B and C) Lens echoes R) Retina. D) Posterior wall

Results

Tables I and II show the length of the posterior segment in boys and in girls During the first year and a half the mean value in boys increases by approx 3 2 mm in girls approx 3 0 From the 2nd to the 13th year the length of the posterior segment increases by approx 2 5 mm in boys approx. 2.3 mm in girls

gives values of 14 5–16 mm in emmetropic adults and Nover & Grote (1965) found values between 14 42 and 15 82 mm in emmetropes aged 25–55 years.

Jansson (1963) gives the error of the method in measurements of the length of the vitreous as 0 032 3 SD = ± 0 096 mm

The object of this study is to investigate the longitudinal growth of the posterior segment of the eye (posterior pole of the lens – posterior wall of the eye) during the growth period and to relate the results to refraction In a later work the results of measurements will be related to the depth of the anterior chamber and to the length of the anterior segment (corneal vertex – posterior pole of the lens)

Material and Method

The material and method used in the study have been described in detail in an earlier work (Larsen 1971 a) The study embraces 80 mature newborns 43 boys and 37 girls and 465 boys and 381 girls in the age group 6 months–13 years, the age group 6 months–7 years being examined under general anaesthetic With the exception of the newborns the examination was performed under cycloplegia induced by cyclopentolate hydrochloride 1 % (Cyclogyl R) The eyes had refraction values between + 5 D and – 5 D those with anisometropia greater than 2 D being excluded from the examination

The velocity of ultrasound in the vitreous at 37°C is approx 1532 m/sec (Jansson 1963) This value has been used in the present study A similar velocity at 37°C was given by Tscehewnenko (1965), who computed the velocity of ultrasound in the vitreous to be 1534 m/sec

The length of the vitreous was computed by multiplying the echo distance by the factor k = 1 03 k being calculated according to the formula previously reported (Larsen 1971 a) When the oscilloscope scale was calibrated with the aid of a water column it was found that the section of the scale above 18 mm was not linear This was taken into consideration in computing the real length of the vitreous a varying addition being made for amplitudes above the 18 mm mark on the scale Fig 1 shows the nomogram for these calculations

When the apparatus was used with maximum amplication (Verstarkung 10) and impulse power (Impulsstärke 5) and with a 6 Mc/5 mm transducer as in this investigation the first echo peak from the posterior wall of the eye appeared to be derived from the retina Fig 2 shows an echogram from a 56 year old man with amotio retinae and a clear echo peak from the detached retina

The accuracy of the measurement results was investigated by 10 different measurements of the right eye of a male emmetrope 35 years of age Mean value of these measurements 15 75 mm SD = 0 035 3 SD = 0 105

15 25–15 49							10	6	10	4	18	26	16	8	4	
15.50–15 74						2			3	5	14	4	6	16	12	2
15 75–15 99									3	7	14		6	6	4	6
16 00–16 24								2	1	2	2	4		4	6	8
16 25–16 49								2	2		4		8		12	4
16 50–16 74												4		8	10	4
No of eyes	86	2	4	36	118	110	100	64	64	70	100	80	56	52	56	24
Mean	10 48	11 64	11 94	13 6?	13 79	14 15	14 55	14 73	14 94	14 94	15 22	15 33	15 44	15 59	15 88	16 09
SD	0 41	–	–	0 47	0 50	0 54	0 52	0 61	0 52	0 62	0 58	0 47	0 59	0 76	0 60	0 33
SF	0 044	–	–	0 078	0 046	0 051	0 052	0 076	0 065	0 074	0 058	0 054	0 079	0 105	0 080	0 067

Table I

Length of the vitreous in the present male series SD = standard deviation SE = standard error

Length of vitreous mm	Age															
	Days	Months								years						
	1–5	6	9	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–11	11–12	12–13	13–14
9 75– 9 99	7															
10 00–10 24	17															
10 25–10 49	13															
10 50–10 74	28															
10 75–10 99	12															
11 00–11 24	6															
11 25–11 49	1															
11 50–11 74	2	2	1													
11 75–11 99			1													
12 00–12 24			2													
12 25–12 49					2											
12 50–12 74				2	4											
12 75–12 99					2											
13 00–13 24				6	12	8	4									
13 25–13 49				8	14	5	2	2		2						
13 50–13 74				8	16	8	2		1					2		
13 75–13 99				4	32	22	2	2	3		4			2		
14 00–14 24				3	10	23	11	6	4	4	2					
14 25–14 49				3	23	17	38	17	12	14	6		4			
14 50–14 74				2	3	9	8	8	2	7	12	12	4		2	
14 75–14 99						9	8	7	8	11	16	8			4	
15 00–15 24						7	15	12	15	14	8	22	12	6	2	

14 50–14 74					2	4	[illegible]	6	6	7	4	10	10	8	16	2
14 75–14 99					4	3	3	6	4	2	4	4	8	4	4	
15 00–15 24					2	5	2		4	7	12	4	10	8	14	8
15 25–15 49									7	5	8	12	6	16	6	8
15 50–15 74									1	4		6	2	4	12	12
15 75–15 99										2		4	4		8	16
16 00–16 24													4	12	8	
16 25–16 49										2				8		
16 50–16 74														2		
16 75–16 99														2		
17 00–17 24																
17 25–17 49									2							
No of cycs	74	2	2	22	104	90	66	46	64	50	32	48	44	72	76	48
Mean	10 2[illegible]	11 64	12 05	13 24	13 72	13 97	14 18	14 [illegible]3	14 52	14 74	14 98	15 14	15 11	15 39	15 34	15 59
SD	0 5[illegible]	–	–	0 44	0 50	0 [illegible]8	0 49	0 39	0 73	0 62	0 33	0 49	0 48	0 68	0 64	0 38
SE	0 060	–	–	0 094	0 049	0 061	0 060	0 058	0 091	0 088	0 058	0 071	0 072	0 086	0 073	0 055

Table 11

Length of the vitreous in the present female series SD = standard deviation SE = standard error

Length of vitreous mm	Age															
	Days	Months		years												
	1–5	6	9	1–2	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10	10–11	11–12	12–13	13–14
< 9 25	2															
9 25– 9 49	4															
9 50– 9 74	4															
9 75– 9 99	16															
10 00–10 24	21															
10 25–10 49	11															
10 50–10 74	6															
10 75–10 99	6															
11 00–11 24	1															
11 25–11 49	1															
11 50–11 74		2														
11 75–11 99	2															
12 00–12 24			2													
12 25–12 49				1												
12 50–12 74				5		2										
12 75–12 99					2											
13 00–13 24				6	26	6	5									
13 25–13 49				2	6	16	7	2								
13 50–13 74				4	23	12	10	1	2							
13 75–13 99				4	21	10	10	11	9	2						
14 00–14 24					8	11	8	6	9	10				2		
14 25–14 49					10	21	16	14	20	[illegible]	4	8		10	4	2

Table III

Length of the vitreous in age groups (mean values) and the difference between the sexes *Test of significance* Student T test

		Age				
		Days 1–5	Years 1–2	3–6	7–9	10–13
Length of vitreous *mm* (mean)	Boys	10 48	13 62	14 34	15 12	15 62
	Girls	10 22	13 24	14 05	14 89	15 31
Differences mm		0 26	0 38	0 29	0 23	0 31
P values		P < 0 01	P < 0 01	P < 0 01	0 01 < P < 0 05	P < 0 01
No of *eyes*	Boys	66	36	456	250	188
	Girls	74	22	370	130	240

Fig 4 shows the growth curve for this age group for the emmetropic hypermetropic and myopic infants *respectively* and also for emmetropic boys and girls. There were so few myopic children that separate curves for boys and girls would not have given a realistic picture The mean value in myopic children in this age group is approx 0 3–0 6 mm higher than the mean value in emmetropes, which is again from 0 1–0 2 mm higher than that in hypermetropes The difference in mean value between myopic and emmetropic children is probably significant (0 01 < P < 0 05) and also significant between emmetropic and hypermetropic children (P < 0 01)

The sex linked difference in the length of the vitreous is reflected in the values for the different forms of refraction The difference in mean value between hypermetropic boys and girls is significant (P < 0 01) the difference between emmetropic boys and girls probably significant (0 01 < P < 0 05)

In older children it was only in the year class of 12 year old girls (76 eyes) that the dispersion in refraction was great enough (values between + 5 D and −5 D) to be capable of giving realistic values in statistical computation of the relationship between the length of the vitreous (y) and refraction (x) The correlation was significantly negative as for the relationship between the depth of the anterior chamber and refraction in the same age group

These values are approximately the same as those for adults in the age group 20–40 years, in which the mean value in 10 emmetropic men was 15 44 mm and in 10 emmetropic women 15 18 mm

The growth of the posterior segment is shown in Fig 3 which describes an asymptotic curve As the curve shows, the mean value of the measurement results in all age groups is higher in boys than in girls Table III shows the differences in mean values between the two sexes This difference appears to be already established at birth Throughout the whole growth period the difference in mean value between the sexes is from 0 2–0 4 mm in all age groups As it appears from Table III the difference in mean value is probably significant in the age group 7–9 years (0 01 $< P <$ 0 05) in the remaining age groups including newborns the difference was significant ($P <$ 0 01) The relation between refraction and the length of the vitreous was investigated in infants in the age group 1–3 years which had the greatest relative dispersion of refraction (Larsen 1971 a, Tables IV and V) The age group included 28 myopic eyes 192 emmetropic eyes and 260 hypermetropic eyes the following mean values being found for the different forms of refraction

	Myopia	Emmetropia	Hypermetropia
Boys	14 13 mm	14 04 mm	13 72 mm
Girls	14 24 mm	13 86 mm	13 67 mm

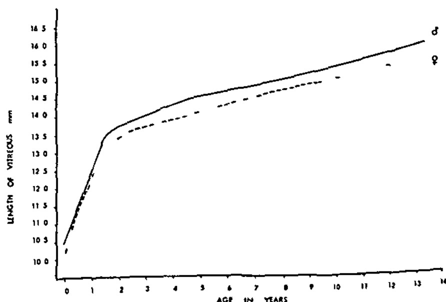


Fig 3
Growth curve (mean values) for the length of the vitreous

Table III

Length of the vitreous in age groups (mean values) and the difference between the sexes
Test of significance Student T test

		Age				
		Days 1–5	Years 1–2	2–6	7–9	10–13
Length of vitreous mm (mean)	Boys	10.48	13.62	14.34	15.12	15.62
	Girls	10.22	13.24	14.05	14.89	15.31
Differences mm		0.26	0.38	0.29	0.23	0.31
P values		P < 0.01	P < 0.01	P < 0.01	0.01 < P < 0.05	P < 0.01
No. of eyes	Boys	86	36	456	250	158
	Girls	[illegible]4	[illegible]2	3[illegible]0	130	240

Fig 4 shows the growth curve for this age group for the emmetropic hypermetropic and myopic infants respectively and also for emmetropic boys and girls. There were so few myopic children that separate curves for boys and girls would not have given a realistic picture. The mean value in myopic children in this age group is approx. 0.3–0.6 mm higher than the mean value in emmetropes which is again from 0.1–0.2 mm higher than that in hypermetropes. The difference in mean value between myopic and emmetropic children is probably significant (0.01 < P < 0.05) and also significant between emmetropic and hypermetropic children (P < 0.01).

The sex linked difference in the length of the vitreous is reflected in the values for the different forms of refraction. The difference in mean value between hypermetropic boys and girls is significant (P < 0.01), the difference between emmetropic boys and girls probably significant (0.01 < P < 0.05).

In older children it was only in the year class of 12 year old girls ([illegible]6 eyes) that the dispersion in refraction was great enough (values between + 5 D and – 5 D) to be capable of giving realistic values in statistical computation of the relationship between the length of the vitreous (y) and refraction (x). The correlation was significantly negative as for the relationship between the depth of the anterior chamber and refraction in the same age group.

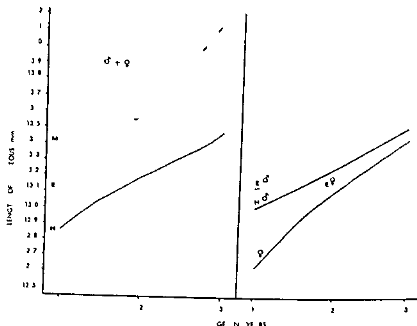


Fig 4
Length of the vitreous for myopic (M) emmetropic (E) and hypermetropic (H) children in the age classes 1–3 years

Line of regression
$y = 15.34 - 0.200 \times$ mm
$r = -0.880$
$\varepsilon r = 0.0552$
$P < 0.001$
The relation is shown graphically in Fig 5

Discussion

In this investigation the mean value for the length of the vitreous in newborns was between 10 and 11 mm This is in good accordance with the values found by Cernet (1964) and Luyckx (1966)

In the course of the first year and a half of life the vitreous increases rapidly in length reaching a mean value of approx 13.6 mm in boys and approx 13.2 mm in girls There is further longitudinal growth of approx 1.3 mm in both sexes from the 2nd to the 7th year and of approx 1.1 mm from the 7th to the 13th year At this age the mean value in boys is 16.09 mm in girls 15.59 mm and the length of the vitreous then appears to have reached the values found in

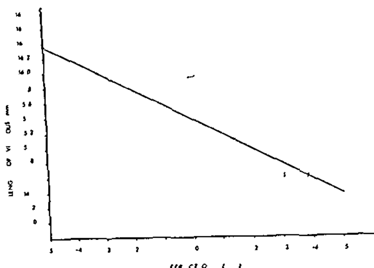


Fig 5
Correlation between length of vitreous and refraction girls age 12 years (/6 eyes)
Regression line y = 15 34–0 °00 × mm

adults Measurements made in *10* emmetropic men and *10 emmetropic women* (age 20–40 years) show values from 14 9–16 0 mm in men and 14 5–15 16 mm in women These values accord well with those found by Jansson (1963) Gernet (1964) and Nover & Grote (1965)

Few workers seem to have investigated the longitudinal growth of the vitreous in the post natal growth period A comparison of the values found in the present study with those given in the growth curve of Gernet & Hollwich shows good accord in the measurement results in older children (12 years) with values of approx 15 5 mm These authors found a relatively rapid increase of the length of the vitreous up to the age of 3 years and a comparatively slow increase of approx 0 5 mm from the age of 3 to 12 years The explanation of the difference found in the growth rate is possibly that these authors had a relatively small material (66 eyes) so that any marginal physiological values present in the age classes may have influenced the form of the curve

Sorsby et al (1963) made ultrasonic measurements of 140 eyes some of this *material consisting of older children with varying ocular refraction* In computing the values for the length of the vitreous the mean value for boys in the age group /–10 years (/ eyes) was 16 63 mm in girls (10 eyes) 15 30 mm In the age group 11–13 years the mean value found in boys (11 eyes) was 16 /9 mm *in girls (13 eyes) 15 92* mm

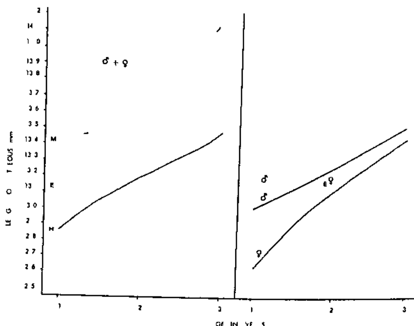


Fig 4
Length of the vitreous for myopic (M) emmetropic (E) and hypermetropic (H) children in the age classes 1–3 years

Line of regression
$y = 15\ 34 - 0\ 200 \times$ mm
$r = -0\ 880$
$\varepsilon r = 0\ 0552$
$P < 0\ 001$
The relation is shown graphically in Fig 5

Discussion

In this investigation the mean value for the length of the vitreous in newborns was between 10 and 11 mm This is in good accordance with the values found by Gernet (1964) and Luyckx (1966)

In the course of the first year and a half of life the vitreous increases rapidly in length reaching a mean value of approx 13 6 mm in boys and approx 13 2 mm in girls There is further longitudinal growth of approx 1 3 mm in both sexes from the 2nd to the 7th year and of approx 1 1 mm from the 7th to the 13th year At this age the mean value in boys is 16 09 mm in girls 15 59 mm and the length of the vitreous then appears to have reached the values found in

of the vitreous had then reached values as for young emmetropic adults It thus seems that the longitudinal growth of the vitreous terminates at the age of 13 or is minimal after this age

At birth and throughout the entire growth period a sex linked difference was found in the length of the vitreous with 0 23–0.38 mm greater mean values in boys

The relationship between the length of the vitreous and refraction with the greatest length being found in myopes and the smallest in hypermetropes is probably developed very early in the growth period and was in this study found to be fully established from the age of one year

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In this study a sex linked difference in the length of the vitreous was found throughout the entire growth period, the values in boys (computed from age groups Table III) being 0.2–0.4 mm greater than those in girls. Although refraction was not measured in newborns it seems unlikely in a material chosen randomly that the sex linked difference in the length of the posterior segment can be attributed to a difference in refraction. On the other hand the results indicate that there is also a sex linked difference in the length of the vitreous in newborns as in the rest of the growth period. This is also indicated by the equally great relative increases from birth to the age of one and a half – between 29 and 30 per cent in both boys and girls, and from one and a half to 7 years by 9.7 per cent. From the age of 7 to 13 the increase in length is between 7 and 8 per cent in both sexes.

In an earlier work (Larsen 1971 b) the distance from the corneal vertex to the posterior pole of the lens was used as an indicator of the length of the anterior segment. It was found that this distance increased from birth to the age of one and a half by an average of 0.69 mm in boys and 0.53 mm in girls. This corresponds to an increase of 10.5 and 8.3 per cent, respectively. After this age the increase was only of the order of 2–3 per cent (0.1–0.2 mm) with a slight increase after the 3rd year of life, and stagnation at the age of 7–8 years. It thus seems that the longitudinal growth of the posterior segment is greater not only in absolute figures but also relatively than that of the anterior segment. *It also seems that the longitudinal growth of the eye after the age of 8 years depends almost exclusively on an increase in the length of the vitreous.*

In newborns Gernet (1964) was unable to demonstrate any relationship between the axial length of the eye and refraction. After the age of about one year, however, this relationship appears to be fully established. Although there was little dispersion (– 2.5 D to + 4.5 D) in the ocular refraction of the infants (1–3 years) in this study there was a significant difference in the length of the vitreous in the different forms of refraction.

Summary

The length of the vitreous was measured ultrasonically in 926 children (1852 eyes). The study embraced 80 newborns (43 boys and 37 girls) and 846 children (465 boys and 381 girls) aged 6 months–13 years. The mean value in newborns was 10.48 mm in boys and 10.22 mm in girls. In the course of the first year and a half of life the length of the vitreous increased by approx. 3.1 mm in boys and 3.0 mm in girls. In both sexes the length increased by approx. 1.3 mm from the 2nd to the 7th year, and by a further 1.1 mm from the 7th to the 13th year. At this age the mean value in boys was 16.09 mm, in girls 15.59 mm, and the length

dans la détermination de la profondeur de la chambre antérieure (Delmarcelle et al 1969 1970 Luyckx & Delmarcelle 1969)

Les observations biométriques montrent que plus le cristallin est épais moins la chambre antérieure est profonde Une partie de cette épaisseur se projette en *arrière vers la cavité vitréenne* l autre partie réduit la profondeur de la chambre antérieure en avançant le pôle antérieur du cristallin a concurrence de 37 pour cent de l épaisseur de la lentille

Chez le sujet normal chaque millimètre du cristallin réduit la profondeur de la chambre antérieure de 0 37 mm suivant la formule profondeur chambre antérieure = 4 44 mm – 37 pour cent épais cristallin Au cours du vieillissement l épaississement de la lentille réduit progressivement la profondeur de la chambre antérieure 0 008 mm par année (Luyckx & Weekers 1966)

En cas de cataracte Weekers et al (1963) *ont observé des valeurs de profondeur* de la chambre antérieure plus dispersées que parmi les yeux normaux L intumescence du cristallin est responsable de l aplatissement de la chambre antérieure tandis que la phacolyse du cristallin hypermature entraîne son approfondissement Le présent travail étudie les modifications de profondeur de la chambre antérieure dans les différents types morphologiques de cataracte sénile

Matériel et techniques

(a) Cent six patients âgés de 50 a 94 ans (âge moyen 70 ans) atteints de cataracte sénile uni ou bilatérale a différents stades d évolution ont été soumis a l examen *biomicroscopique du cristallin et a la mesure optique de la profondeur de la chambre antérieure* (212 yeux) Dans le but de réaliser une étude comparative seuls ont été retenus les sujets présentant une asymétrie dans l importance des opacités du cristallin des deux yeux Cette asymétrie est admise quand deux au moins des trois critères suivants sont réunis différence de lueur pupillaire entre les deux yeux différence d acuité visuelle et différence d intensité ou de dimension des opacités a l examen biomicroscopique de la cataracte

La profondeur de la chambre antérieure est mesurée par l oculaire biométrique de la lampe a fente de Haag Streit modèle 900 (Lowe 1966) sans dilatation pupillaire préalable

(b) La mesure directe de l épaisseur du cristallin par *méthode échographique* a en outre été réalisée chez vingt sept sujets atteints de cataracte asymétrique a l aide de l ultrasonographe de Kretz (modèle 7000) equipé d une sonde de 5 mm de diamètre et d une fréquence de 10 MHz suivant la technique décrite par Luyckx & Weekers en 1966 L ultrasonographie permet une mesure assez précise de l épaisseur du cristallin *in situ* (Oksala & Salminen 1963) bien que la présence d une cataracte puisse faire apparaître des échos supplémentaires aux *interfaces*

Clinique Ophtalmologique de l Université de Liege Belgique
(Directeur Prof R Weekers)

BIOMETRIE DU SEGMENT ANTERIEUR DANS LA CATARACTE SENILE

Par

Y DELMARCELLE & J LUYCKX BACUS

Introduction

Chez le sujet normal le cristallin augmente de volume avec l age et son diamètre antero postérieur s accroit (Raeder 1922 Huggert 1946) L échographie ultrasonique permet de deceler *in vivo* une correlation significative entre l age du sujet et l epaisseur du cristallin (Jansson 1963) D après Luyckx & Weekers (1966) l epaisseur du cristallin augmente de 0 018 mm par annee d age Cette augmentation de volume resulte de l apposition continue de nouvelles fibres cristalliniennes corticales dont l effet biometrique est partiellement compensé par la condensation des fibres centrales (Vogt 1931) En 1946 deja Huggert avait conclu a un epaississement de la corticale de 0 007 mm par annee

L apparition d une cataracte modifie cette evolution L intumescence du cristallin s accompagne d une augmentation parfois très rapide du volume de la lentille La phacolyse stade ultime d evolution d une cataracte senile entraine un aplatissement cristallinien Dans la cataracte présénile unilatérale Goldmann & Favre (1961) ont mis en evidence par une méthode optique une reduction d epaisseur du noyau adulte et du cortex tandis que Goldmann & Niesel (1964) observent un amincissement du cristallin dès le debut de la cataracte sénile Babel et al (1969) confirment par ultrasonographie cet amincissement de la lentille dans la cataracte presénile et senile unilaterale

L endroit d insertion du cristallin et son épaisseur jouent un role important

Received January 12 1971

profondit de façon significative au cours du developpement d une cataracte senile (t = 5 1 et 2 8) Cet approfondissement s observe dans 87 pour cent des cas La dispersion des valeurs de chambre anterieure est la plus large dans les yeux les plus cataractés

(?) Le Tableau I represente les profondeurs de chambre anterieure en fonction du type et de l importance de la cataracte L aspect morphologique de la cataracte n influence pas la profondeur de la chambre anterieure si ce n est en fonction de l importance de cette cataracte Dans les cataractes plus avancees (groupe 1) les formes *corticales nucleaires* et *cortico nucleaires* ont des chambres antérieures comparables (3 01 mm 2 95 mm et 3 02 mm) Il en est de meme dans les yeux moins atteints (groupe 2 2 73 mm 2 69 mm et 2 69 mm)

Par contre l augmentation progressive de l intensite de la cataracte influence la profondeur de la chambre anterieure dans chacun de ces trois types morphologiques Dans la cataracte *totale* stade le plus evolue la chambre anterieure est la plus profonde 3 16 mm Les yeux atteints de cataracte en *soucoupe posterieure* ou de *sclerose diffuse* du cristallin presentent aussi une augmentation de

Tableau I

Profondeur de la chambre anterieure dans differents types morphologiques de cataracte senile à divers stades d evolution

Type de cataracte	Age Moyen (ans)	Profondeur de chambre anterieure (mm)	
		Groupe 1 cataracte + importante	Groupe 2 cataracte – importante
Totale	73½	3 16 ± 0 34 (38 yeux)	2 85 (3 yeux)
Cortico nucléaire	7?	3 02 ± 0 49 (13 yeux)	2 69 ± 0 44 (14 yeux)
Corticale	70½	3 01 ± 0 37 (0 yeux)	2 73 ± 0 37 (?3 yeux)
Nucleaire	71	2 95 ± 0 41 (34 yeux)	2 69 ± 0 33 (?4 yeux)
Soucoupe postérieure	66	3 45 (1 oeil)	3 09 ± 0 2 (6 yeux)
Sclérose diffuse modérée	70	–	2 89 ± 0 35 (14 yeux)
Yeux congeneres normaux	68	–	2 86 + 0.32 (? yeux)
Total		3 05 ± 0 39 (106 yeux)	2 78 ± 0.36 (106 yeux)

cortex noyau du cristallin (Oksala & Varonen 1965) La vitesse de propagation des ultrasons étant reduite de maniere variable dans le cristallin cataracté (Jansson & Kock 1962), il peut en resulter une erreur de 0 2 a 0 3 mm dans la mesure de l épaisseur de la lentille (Babel et al 1969)

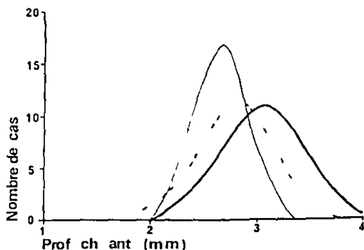
Résultats

Biométrie optique

(1) Le graphique 1 représente la *répartition des profondeurs de chambre antérieure* chez cinquante sujets normaux (100 yeux) de meme age moyen (69 ans) et chez 106 patients (212 yeux) atteints de cataracte sénile asymétrique répartis en deux groupes suivant l importance de la cataracte le premier groupe est constitue par les yeux les plus cataractes (acuite visuelle 0 1 refraction moyenne – 2 dioptries) le second groupe rassemble les yeux adelphes moins cataractes (acuite visuelle 0 5 refraction moyenne 0 dioptrie)

Du cote ou la cataracte est la plus dense la profondeur moyenne de la chambre antérieure est de 3 05 mm (± 0 39 mm) du cote le moins cataracté elle est de 2 78 mm (± 0 36 mm) Dans le matériel controle de meme âge sans cataracte la profondeur de chambre anterieure est de 2 66 mm (± 0 24 mm)

La comparaison de ces trois groupes montre que la chambre antérieure s ap



Graphique 1
Repartition des profondeurs de chambre anterieure de l oeil normal et l oeil cataracte ——— sujets normaux de meme age (100 globes) 2 66 mm ± 0 24 ---- yeux les moins cataractés (106 globes) 2 78 mm ± 0 36 ——— yeux congénères plus cataractes (106 globes) 3 05 mm ± 0 39 Ces trois repartitions sont statisquement différentes (t = 5 1 et 2 8)

profondit de façon significative au cours du développement d une cataracte senile (t = 5 1 et 2 8) Cet approfondissement s observe dans 87 pour cent des cas La dispersion des valeurs de *chambre anterieure* est la plus large dans les yeux les plus cataractes

(9) Le Tableau I represente les profondeurs de chambre anterieure en fonction du type et de l importance de la cataracte L aspect morphologique de la cataracte n influence pas la profondeur de la chambre anterieure si ce n est en fonction de l importance de cette cataracte Dans les cataractes plus avancees (groupe 1) les formes *corticales nucleaires* et *cortico nucleaires* ont des chambres antérieures comparables (3 01 mm 2 95 mm et 3 02 mm) Il en est de meme dans les yeux moins atteints (groupe 2 2 73 mm 2 69 mm et 2 69 mm)

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Tableau I

Profondeur de la chambre antérieure dans differents types morphologiques de cataracte senile a divers stades d'evolution

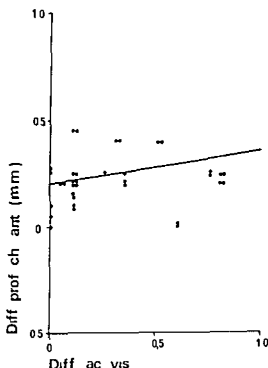
Type de cataracte	Age Moyen (ans)	Profondeur de chambre antérieure (mm)	
		Groupe 1 cataracte + importante	Groupe 2 cataracte – importante
Totale	[illegible]	3 16 ± 0.34 (38 yeux)	2 85 (3 yeux)
Cortico nucléaire	[illegible]	3 02 ± 0 49 (13 yeux)	2 69 ± 0 44 (14 yeux)
Corticale	[illegible]	3 01 ± 0.3[illegible] ([illegible]0 yeux)	2 73 ± 0.3[illegible] (23 yeux)
Nucleaire	71	2 95 ± 0 41 (34 yeux)	2 69 ± 0.33 (24 yeux)
Soucoupe posterieur	66	3 45 (1 oeil)	3 09 ± 0 2 (6 yeux)
Sclérose diffuse moderee	[illegible]0	–	2 89 ± 0 35 (14 yeux)
Yeux non degeneres normaux	68	–	2 86 + 0.32 ([illegible] yeux)
Total	[illegible]	3 05 ± 0.39 (106 yeux)	2 78 ± 0.36 (106 yeux)

la profondeur de la chambre antérieure (3 09 mm et 2 89 mm) bien que l anoma lie soit morphologiquement peu étendue en cas de soucoupe postérieure ou peu dense dans la sclérose nucléaire

Dans les *22 yeux normaux* congenères de cataracte unilatérale la profondeur de chambre anterieure est de 2 86 mm valeur plus élevée que chez le sujet nor mal de meme age (2 66 mm)

(3) L approfondissement de la chambre anterieure en fonction de l importance de la cataracte est confirme par la *relation entre l ecart des acuites visuelles des deux yeux* (temoin de l importance de la cataracte) *et la difference de profon deur de la chambre anterieure des deux yeux* (Graph 2) l importance de la chute d acuite visuelle est proportionnelle a l approfondissement de la chambre anterieure (y = 0 21–0 15 ×) malgré une grande dispersion des valeurs

Cette relation existe dans les differents groupes morphologiques de cataracte (Tableau II) Dans les cataractes nucléaires peu avancées (A V 0 45) la pro fondeur de chambre antérieure est de 2 69 mm tandis que dans le groupe plus atteint (A V 0 15) elle est de 2 95 mm Dans les cataractes corticales la pro



Graphique 2

Relation entre l ecart d acuite visuelle des deux yeux et l approfondissement de la chambre anterieure dans la cataracte senile (103 paires d yeux) (y = 0 21 – 0 15 × r = – 0 20)

Tableau II

Acuité visuelle et profondeur de chambre antérieure en fonction du type morphologique et l'importance de la cataracte Il existe une relation significative entre la chute d'acuité visuelle témoin de l'importance de la cataracte et l'approfondissement de la chambre antérieure

Type de cataracte	Nombre de cas	Acuité visuelle	Refraction (dioptrie)	Profondeur chambre anterieure (mm)
Nucléaire + dense	34	0 15	− 3.5	2 95
— dense	24	0 45	− 1.3	2 69
Corticale + dense	20	0.30	− 1	3 01
— dense	23	0 45	0	2 73

fondeur de chambre anterieure est de 2 73 mm et l acuite visuelle moyenne de 0 45 tandis qu elle est de 3 01 mm avec une vision moyenne de 0 30

(4) En cas de cataracte importante il n existe plus de correlation significative entre *l'age du sujet et la profondeur de la chambre anterieure* contrairement a ce que l on observe chez le sujet normal (Graph 3) L apparition d une cataracte attenue donc ou supprime la reduction progressive de la chambre anterieure en fonction de l age que l on observe chez le sujet normal a lentille transparente Cette relation peut meme s inverser si la cataracte devient importante a age egal on trouve en effet un approfondissement de la chambre anterieure d autant plus marqué que la cataracte est avancee

(5) Il n y a pas de relation significative entre *l age du sujet et le type de cataracte* (Tableau I) Les sujets sont un peu moins ages (68 ans) lorsque le cristallin est transparent d un cote et l age est plus avance dans la cataracte totale ou cortico nucléaire (73 ans et 76 ans)

(6) Dans les yeux atteints de cataracte il n y a pas de relation entre *la profondeur de la chambre anterieure et la refraction* Rappelons que chez le sujet normal la chambre anterieure est plus profonde chez le myope que chez l hypermetrope car il s agit d ametropies axiles

Biométrie ultrasonique

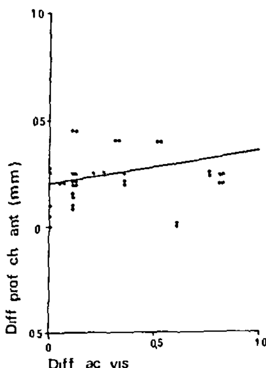
Le Tableau III groupe les resultats obtenus chez dix sept sujet atteints de cataracte senile bilaterale d importance differente aux deux yeux L oeil le plus atteint presente dans tous les cas une cataracte totale l oeil congénere une cataracte nucleaire ou corticale debutante

la profondeur de la chambre anterieure (3 09 mm et 2 89 mm) bien que l anomalie soit morphologiquement peu étendue en cas de soucoupe postérieure ou peu dense dans la sclérose nucléaire

Dans les 22 *yeux normaux* congéneres de cataracte unilatérale la profondeur de chambre anterieure est de 2 86 mm valeur plus élevée que chez le sujet normal de meme age (2 66 mm)

(3) L approfondissement de la chambre anterieure en fonction de l importance de la cataracte est confirme par la *relation entre l ecart des acuites visuelles des deux yeux* (temoin de l importance de la cataracte) *et la différence de profondeur de la chambre anterieure des deux yeux* (Graph 2) l importance de la chute d acuite visuelle est proportionnelle a l approfondissement de la chambre anterieure (y = 0 21–0 15 x) malgré une grande dispersion des valeurs

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Graphique 2
Relation entre l ecart d acuite visuelle des deux yeux et l approfondissement de la chambre anterieure dans la cataracte senile (103 paires d yeux) (y = 0 21 – 0 15 x r = – 0 20)

- dix sujets présentant une cataracte intumescente unilaterale l oeil congenere etant normal

Les mesures optiques de la profondeur de la chambre anterieure et ultrasoniques de l épaisseur du cristallin de la longueur de la cavite vitréenne et de la longueur totale du globe mettent en évidence

(1) *Dans la cataracte totale banale*

- un approfondissement de la chambre anterieure de 0 35 mm par rapport aux valeurs normales compte tenu de l age et de 0 20 mm par rapport a l oeil congenere moins atteint
- une diminution de l epaisseur du cristallin de 0 60 mm par rapport aux valeurs normales et de 0 50 mm par rapport a l oeil congenere
- un allongement de la cavite vitreenne de 0 40 mm dans l oeil le plus atteint et de 0 20 mm dans l oeil congénere par rapport aux valeurs normales

L oeil congenère moins cataracte presente donc les memes alterations biometriques que l oeil le plus atteint mais a un degre moindre

(2) *Dans la cataracte intumescente*

l evolution est inverse la lentille s epaissit de 0 85 mm reduisant la profondeur de la chambre antérieure de 0 60 mm et la cavite vitreenne de 0 40 mm *

Commentaires biometriques

Le cristallin croit au cours de l existence des fibres nouvelles corticales se forment constamment a partir de la zone germinative equatoriale Malgre une condensation centrale il en resulte un epaississement progressif de la lentille avec l age entrainant une reduction de profondeur de la chambre anterieure.

L apparition d une cataracte senile modifie cette evolution biométrique

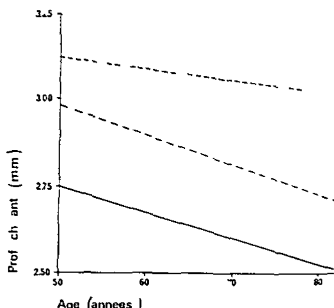
(a) L étude comparative de 106 sujets atteints de cataracte sénile asymetrique a divers stades d evolution revele que *la cataracte senile provoque dans 87 pour cent des cas un approfondissement de la chambre anterieure*

(1) l augmentation de profondeur de chambre anterieure est *proportionnelle a l importance de la cataracte* ainsi qu en témoignent

(α) la comparaison des profondeurs de chambre anterieure entre les deux yeux d un meme sujet (Tableau I) l oeil le plus cataracte présente en general la chambre anterieure plus profonde Cette observation a d autant plus de signi

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* Dans trois cas de cataracte intumescente Babel et al (1969) trouvent des epaisseurs du cristallin comparables 5 0 mm a 5 5 mm



Graphique 3
Relation entre la profondeur de la chambre antérieure et l'âge du sujet dans l'oeil normal et l'oeil cataracté ——— oeil normal $y = 3.15 - 0.008x$ ($r = -0.50$) - - cataracte importante (groupe 2) $y = 3.41 - 0.009x$ ($r = -0.20$) ---- cataracte complète (groupe 1) $y = 3.29 - 0.005x$ ($r = 0.074$ non significatif)

Tableau III
Biométrie ultrasonique et optique dans 27 cas de cataracte asymétrique

Type de cataracte	Biométrie (mm)			
		Sujet normal (de même âge)	Cataracte totale	Cataracte débutante ou absente
Sénile banale 17 cas (âge moyen 73 ans)	Prof ch antér *	2.55	*2.90*	2.[illegible]0
	Ep cristallin	5.00	*4.40*	4.90
	long vitré	16.25	16.65	16.45
	long totale globe+	24.50	24.45	24.55
Intumescente 10 cas (âge moyen 64 ans)	Prof ch antér *	2.65	*2.05*	2.60
	Ep cristallin	4.95	*5.50*	4.85
	long vitré	16.85	15.95	16.45
	long totale globe+	24.45	24.40	24.40

* biométrie optique
\+ compris l'épaisseur de la cornée

Tableau IV

Position et épaisseur du cristallin dans 11 cas de cataracte sénile totale L aplatissement du cristallin cataracté (0 60 mm) se repartit de manière à peu pres symetrique au niveau de ses deux faces (0 35 mm et 0 25 mm)

	Sujet normal	Cataracte totale	Difference
Position face anter cristallin (mm) (= prof ch anter)	2.55	2 90	− 0.35
Position face poster cristallin (mm)	7 55	7.30	− 0 25
Epaisseur cristallin (mm)	5 00	4 40	− 0 60

surtout si elle est totale, la face antérieure du cristallin recule (moyenne 0 35 mm) tandis que sa face posterieure avance (moyenne 0 25 mm) Ces deux phenomenes resultent d un amincissement de la lentille (0 60 mm)

Le nombre de cas n est pas suffisant pour savoir

– si cet amincissement se repartit de maniere differente au niveau de la face antérieure et postérieure de la lentille

– s il existe une modification de la position d insertion du cristallin en rapport avec une altération du zonule Lowe (1970) constate au cours du vieillissement normal du cristallin un avancement progressif de son insertion atteignant 0 2 mm Nous n avons pu confirmer cette observation chez le sujet normal (Delmarcelle et al 1969 1970)

(c) Dans la cataracte intumescente par contre la position de la face anterieure du cristallin avance de 0 60 mm tandis que sa face posterieure recule de 0 25 mm un épaississement global de la lentille de 0 85 mm en résulte (Tableau V)

Tableau V

Position et epaisseur du cristallin dans 10 cas de cataracte senile intumescente L epaississement de la lentille en cas de cataracte intumescente modifie surtout la position de sa face antérieure.

	Sujet normal	Cataracte intumescente	Difference
Position face anter cristallin (mm) (= prof ch anter)	2 65	2 05	+ 0 60
Position face poster cristallin (mm)	7 60	7 85	+ 0 25
Epaisseur cristallin (mm)	4 95	5 80	+ 0 85

fication que chez le sujet normal, les deux yeux ont presque toujours la meme profondeur de chambre anterieure

(β) la relation significative entre la chute d'acuite visuelle temoin de l'importance de la cataracte et la profondeur de la chambre anterieure (Tableau II et Graph 2)

(γ) la presence des chambres anterieures les plus profondes en cas de cataracte totale

(2) cette evolution biometrique est *comparable dans les differents types morphologiques de cataracte senile* nucleaire corticale ou mixte (Tableaux I et II) Dans la cataracte totale stade evolutif ultime des formes precédentes l'approfondissement est le plus important Les cataractes en soucoupe posterieure bien que morphologiquement tres localisées s'accompagnent d une augmentation significative de la profondeur de la chambre anterieure Il en est de meme en cas de sclerose diffuse moderee de la lentille

(3) l alteration biometrique de la chambre anterieure en cas de cataracte senile intervient donc *precocement*

De plus il semble que les yeux congeneres « normaux » des patients atteints de cataracte senile unilaterale presentent egalement un approfondissement de la chambre anterieure

Les cataractes séniles devenant presque toujours bilatérales il est probable que l arret de croissance des fibres cristalliniennes précede l apparition des opacites du cristallin cliniquement visibles Un examen biomicroscopique attentif de ces cas permet souvent de deceler des modifications discrètes du cristallin vacuoles sous capsulaires anterieures ou sclerose diffuse Il est difficile de savoir si ces alterations sont plus frequentes que celles observées chez le sujet normal de meme age (Cinotti & Path 1968 Schaffer & Rosenthal 1970)

(4) cette augmentation de profondeur de la chambre anterieure bien que survenant precocement ne se poursuit que tres *lentement* En un an d apres l experience recueillie dans nos cas il n y a pas de modification appréciable de la profondeur de chambre anterieure dans la plupart des cas Une variation biometrique rapide est exceptionnelle Nous en avons rapporte quelques observations dans une publication anterieure (Delmarcelle & Luyckx 1970)

Dans les *cataractes diathesiques ou traumatiques* l evolution est différente la chambre anterieure se reduit généralement et l évolution biometrique est plus rapide
Nous avons observe d importantes variations de chambre anterieure en quelques mois ou meme en quelques semaines dans des cataractes en rapport avec differentes affections hypocalcemie dystrophie myotonique intoxication par dinitrophénol ou traumatisme

(b) *Cet approfondissement de la chambre anterieure correspond a un aplatissement de la lentille* (Tableau IV)

Les donnees echographiques montrent que dans la cataracte sénile banale

Tableau IV

Position et epaisseur du cristallin dans 17 cas de cataracte senile totale L aplatissement du cristallin cataracte (*0 60 mm*) *se répartit de manière à peu pres symetrique* au niveau de ses deux faces (0 35 mm et 0 25 mm)

	Sujet normal	Cataracte totale	Difference
Position face anter cristallin (mm) (= prof ch anter)	2 55	2 90	−0.35
Position face poster cristallin (mm)	7.55	7.30	−0 25
Epaisseur cristallin (mm)	5 00	4 40	−0 60

surtout si elle est totale la face anterieure du cristallin recule (moyenne 0 35 mm) tandis que sa face posterieure avance (moyenne 0 25 mm) Ces deux phenomenes resultent d un amincissement de la lentille (0 60 mm)

Le nombre de cas n est pas suffisant pour savoir

– si cet amincissement se repartit de maniere differente au niveau de la face anterieure et posterieure de la lentille

– s il existe une modification de la position d insertion du cristallin en rapport avec une alteration du zonule Lowe (1970) constate au cours du vieillissement normal du cristallin un avancement progressif de son insertion atteignant *0 2 mm* Nous n avons pu confirmer cette observation chez le sujet normal (Delmarcelle et al 1969 1970)

(c)*Dans la cataracte intumescente* par contre la position de la face anterieure du cristallin avance de *0 60 mm tandis que sa face* posterieure recule de *0 25* mm un epaississement global de la lentille de 0 85 mm en resulte (Tableau V)

Tableau V

Position et epaisseur du cristallin dans 10 cas de cataracte senile intumescente L epaississement de la lentille en cas de cataracte intumescente modifie surtout la position de sa face antérieure.

	Sujet normal	Cataracte intumescente	Difference
Position face anter cristallin (mm) (= prof ch anter)	2 65	2 0	+ 0 60
Position face poster cristallin (mm)	7 60	7 85	+ 0 25
Epaisseur cristallin (mm)	4 95	5 80	+ 0 85

fication que chez le sujet normal les deux yeux ont presque toujours la meme profondeur de chambre anterieure

(β) la relation significative entre la chute d acuité visuelle temoin de l importance de la cataracte et la profondeur de la chambre antérieure (Tableau II et Graph 2)

(γ) la presence des chambres anterieures les plus profondes en cas de cataracte totale

(2) cette evolution biometrique est *comparable dans les differents types morphologiques de cataracte senile* nucleaire corticale ou mixte (Tableaux I et II) Dans la cataracte totale stade evolutif ultime des formes precédentes l approfondissement est le plus important Les cataractes en soucoupe postérieure bien que morphologiquement tres localisees s accompagnent d une augmentation significative de la profondeur de la chambre anterieure Il en est de meme en cas de sclerose diffuse moderee de la lentille

(3) l alteration biométrique de la chambre anterieure en cas de cataracte senile intervient donc *precocement*

De plus il semble que les yeux congeneres « normaux » des patients atteints de cataracte senile unilaterale presentent également un approfondissement de la chambre anterieure

Les cataractes seniles devenant presque toujours bilatérales il est probable que l arret de croissance des fibres cristalliniennes precede l apparition des opacites du cristallin cliniquement visibles Un examen biomicroscopique attentif de ces cas permet souvent de déceler des modifications discretes du cristallin vacuoles sous capsulaires antérieures ou sclerose diffuse Il est difficile de savoir si ces alterations sont plus frequentes que celles observées chez le sujet normal de meme age (Cinotti & Path 1968 Schaffer & Rosenthal 1970)

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Les données echographiques montrent que dans la cataracte senile banale

s accompagne dans 87 pour cent des cas d un approndissement de la chambre anterieure (a) d autant plus marque que la cataracte est importante (b) inde pendant du type morphologique de cataracte senile Cette evolution est acce leree et plus marquee en cas de phacolyse Elle est inversee en cas d intume scence de la lentille

(?) *les donnees echographiques* confirment que ces variations de profondeur de la chambre antérieure sont secondaires a *des modifications en sens inverse de* l epaisseur du cristallin Dans l intumescence du cristallin il faut tenir compte en outre d une modification de la forme du cristallin qui tend vers la sphéricite

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La face anterieure du cristallin s avance plus que la face posterieure recule l augmentation d epaisseur se repartit a concurrence de 70 pour cent vers l avant et 30 pour cent vers l arriere Cette observation peut s expliquer par une modification de la forme du cristallin qui tend a devenir spherique en cas d intumescence La courbure du cristallin normal etant moins marquee au niveau de sa face anterieure (rayon de courbure 10 mm) que de sa face posterieure (rayon de courbure 6 mm) l evolution vers une forme plus spherique modifie davantage la position de la face antérieure

Interet clinique

La mesure de la profondeur de la chambre anterieure dans la cataracte presente un interet clinique Nous avons montre precedemment (Delmarcelle & Luyckx 1970) que cette mesure permet

1 *d orienter le diagnostic etiologique* Dans la cataracte sénile banale la profondeur de la chambre antérieure est généralement plus grande et elle ne se modifie que tres lentement Une évolution de plusieurs annees est necessaire pour observer des variations mesurables Dans la cataracte diathesique par contre la chambre anterieure est souvent moins profonde et les variations de profondeur sont plus rapides

2 *de surveiller l evolution* La constatation d une variation rapide de profondeur de la chambre antérieure en cas de cataracte senile fait craindre l apparition d une intumescence si la chambre anterieure se reduit ou d une phacolyse si elle s approfondit

3 *de preciser la ligne de conduite therapeutique* L apparition d une intumescence ou d une phacolyse peut rendre necessaire une extraction plus précoce de la lentille La presence d une chambre anterieure etroite contre indique l emploi de mydriatiques qui seraient indiques dans un but optique

La profondeur de la chambre anterieure est egalement intéressante a connaitre au moment de l acte chirurgical D apres Weekers et al (1963) le pourcentage d extractions totales par la ventouse ou la pince est moins important quand la chambre antérieure est etroite L extraction du cristallin par cryo congelation est peu influencee par ce facteur Il est cependant interessant de savoir si le cristallin a extraire est gros ou mince la ligne de conduite per opératoire en est facilitee

En conclusion

(1) *la biometrie optique* de 106 patients atteints de cataracte senile asymetrique et de 50 sujets normaux de meme age permet d etablir que la cataracte sénile

Department of Ophthalmology
the State Hearing Centre and the Institute of Pathology
Århus Kommunehospital University of Århus 8000 Århus C Denmark

CENTRAL CORNEAL THICKNESS IN RETINAL DETACHMENT

BY

F KRUSE HANSEN N EHLERS O BENTZEN and H SØGAARD

In a previous study of central corneal thickness and intraocular pressure in patients with unilateral retinal detachment the difference in pressure between the two eyes was found to be correlated to the difference in thickness between the two corneae (Ehlers & Riise 1967) It was however not until the methods of measurement and the normal range of central corneal thickness had been further investigated (Ehlers & Kruse Hansen 1971 Kruse Hansen 1971) that the observed values were realized to be significantly lower than normal

The purpose of the present investigation therefore has been to measure the central corneal thickness in patients with idiopathic retinal detachment During the study it soon became evident that the corneal thickness was lower than normal and consequently a histological study of the skin has been included in an attempt to demonstrate a more generalized abnormality in these patients

Material and Methods

40 consecutively operated cases of retinal detachment (18 women and 22 men) were studied From a comparison with a material previously reported from this clinic by Ehlers & Østerby (1970) the present series may be considered representative for idiopathic retinal detachment Traumatic cases have been excluded from the present material

An ophthalmological examination was made including measurement of the intraocular pressure by applanation tonometry and of the central corneal thickness with the Haag Streit pachometer The procedure followed in the latter measurement has previously been described (Ehlers & Kruse Hansen 1971) Values of corneal thickness will be given as mean ± standard error of mean

In 16 of the cases a histological examination was made of full skin biopsies

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Adresse des auteurs
Clinique Ophthalmologique (Pr R Weekers) Hopital de Baviere
66 Boulevard de la Constitution Liege (Belgique)

Table I

Corneal thickness in retinal detachment

	Right eyes		*Left eyes*	
	Retinal detachment	Reference values*	Retinal detachment	Reference values*
Males	0.494 ± 0.006 (N = 20)	0.519 ± 0.003 (N = 40)	0.504 ± 0.006 (N = 17)	0.525 ± 0.003 (N = 48)
	P < 0.001		P < 0.005	
Females	0.456 ± 0.007 (N = 11)	0.520 ± 0.003 (N = 36)	0.511 ± 0.008 (N = 16)	0.525 ± 0.004 (N = 26)
	P < 0.001		P < 0.05	

*Reference values from Kruse Hansen (1971)

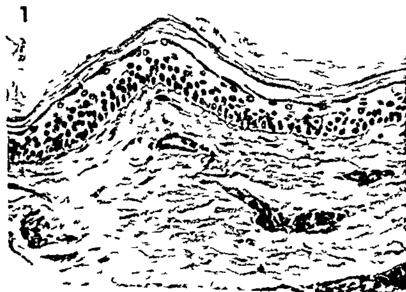


Fig 1

Histological section of skin from patient with retinal detachment Haematoxylin Eosin.

dermal thickness was 1 00 μ the corresponding value of the control group was 1600 μ (Figs 3 & 4)

taken from the anterior side of the femur 20 cm above the patella Similar biopsies from 10 patients without retinal detachment were studied for comparison The biopsies were fixed in neutral buffered 4 % formaldehyde dehydrated in ethanol and embedded in paraffin Sections were stained with haematoxylin eosin van Gieson Hansen Mallory sirius red toluidin blue, Astra blau PAS orcein for elastic fibers and for reticulin a m Foot

Results

The mean value of the intraocular pressure in the 40 eyes with retinal detachment was 12 1 ± 0 7 mm Hg and for the 40 contralateral eyes 13 3 ± 0 7 mm Hg The difference 0 9 mm Hg is not statistically significant

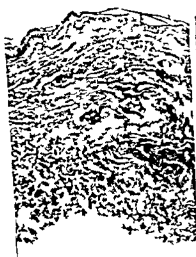
1 Central corneal thickness As central vision is necessary to maintain fixation in the measurement of central corneal thickness both eyes were measured in 23 patients only When the values for corneal thickness in the detachment eye and the contralateral eye were pairwise compared no statistically significant difference was found ($t = 1\ 48$ $0\ 1 < p < 0\ 2$) In the remaining cases only one eye was measured

In the total material (detachment eyes and contralateral eyes) a value of 0 491 ± 0 004 mm was found in 31 right eyes In 33 left eyes a value of 0 508 ± 0 005 mm was found This difference between right and left cornea is explained by the systematic error of measurement caused by the angle kappa (Ehlers & Kruse Hansen 1971) The values for right and left eyes are both significantly lower than our reference values Table I shows the material divided according to sex and laterality Reference values are included The differences between the mean values for the groups of detachment eyes and the corresponding reference values are statistically significant P values are seen from the table

2 Histological examination of the skin When the biopsies from patients with retinal detachment were compared with the controls the rete pegs were found to be flattened the collagenous fibers in the superficial part of the dermis were hypertrophic and the amount of elastic and reticular fibers was reduced In the middle and deeper sheets of the dermis hypertrophic and fragmented collagenous and elastic fibers were found No changes in the mucopolysaccarides of the ground substance were observed The subcutaneous tissue the hairs glands vessels and nerves showed no abnormalities

The mean value for epidermal thickness was 44 μ in the cases of retinal detachment and 58 μ in the control group corresponding to a difference of 10 15 μ or to 1 2 layers of cells (Figs 1 & 2)

The thickness of the dermis was difficult to measure due to great variation within the same section In cases of retinal detachment the mean value of the




Figs 3 and 4 Histological sections of *skin from patient with* retinal detachment (3) and control patient without detachment (4) Haematoxylin Eosin

intraocular pressure (0 9 mm Hg) and indirectly supports the conclusion of Ehlers & Riise (1967) that the difference in thickness in their material was caused by the difference in intraocular pressure

The different pathogenetical theories of retinal detachment (choroidal effusion vitreous degeneration and retinal degeneration with hole) all originate from the last century (von Graefe 1854 Muller 1858 Wecker 1870 Gonin 1904 – cited by Rosengren 1958) and are all still debated (Hervouet 1970) In addition to the demonstration of a reduced thickness of the cornea the present study has also been an attempt to consider the pathogenesis of retinal detachment in relation to generalized abnormalities Degenerative changes in the skin have been observed histologically consisting in thinning of the epidermis and dermis and hypertrophic and fragmented collagenous and elastic fibers Similar histological changes have been demonstrated in otosclerosis by Bentzen (1961) and Stadil (1961) These degenerative changes in the skin and also reduced corneal thickness in the contralateral eyes suggest a universal abnormality of constitution possibly as a pre disposition to development of retinal detachment The rather high incidence of bilateral cases also suggests a universal abnormality Generalized abnormalities have been described previously in familial

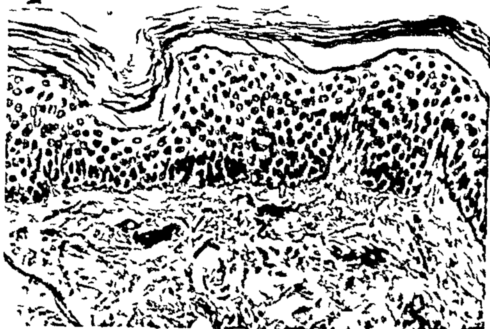


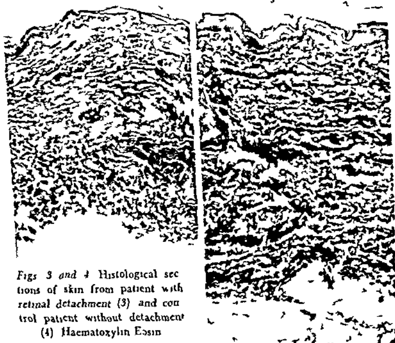
Fig 2
Histological section of skin from control patient without detachment
Haematoxylin Eosin

Discussion

The mean intraocular pressure in the present material is lower than in the reference material in good accordance with statements in the literature The mean intraocular pressure in the contralateral eyes is exactly the same as reported by Ehlers & Osterby (1970) whereas the mean value for the detachment eyes is a little higher This small reduction in pressure in the detachment eyes compared with a reattachment rate of 85 per cent in the present series illustrates the prognostic value of a reduced intraocular pressure in the detachment eye Kruse Hansen (1971) demonstrated within the normal range of intraocular pressure a decreasing corneal thickness with decreasing intraocular pressure. Possibly the lower pressures measured in the contralateral eyes of patients with retinal detachment are caused by the corneal thickness being smaller than normal

No changes with age and sex are normally found in corneal thickness (Kruse Hansen 1971) Consequently a comparison of the present material with the reference material is possible (Table I) and it can be concluded that *the central corneal thickness in retinal detachment is significantly lower than normal*

The lacking difference between corneal thickness of detachment eye and contralateral eye accords well with the small and insignificant difference in



Figs 3 and 4 Histological sections of skin from patient with *retinal detachment (3)* and control patient without detachment (4) Haematoxylin Eosin

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and bilateral retinal detachment (Edmund 1961, Pemberton et al 1966, de Rotth 1939) and have also been described in some interesting case reports (Wolter & McVicar 1966 Epinay et al 1969 Roaf et al 1967 van den Berg 1965 and Delaney et al 1965)

Summary

Forty consecutively operated cases of retinal detachment were studied Central corneal thickness was found to be significantly lower than normal in detachment eyes as well as in contralateral eyes Histological examination of skin biopsies from 17 of the patients revealed from comparison with controls, a smaller thickness of epidermis and dermis and degenerative changes in collagenous and elastic fibers These results suggest a universal abnormality of constitution possibly as a predisposition to development of retinal detachment.

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Department of Neurology (Heads T Fog and H Pakkenberg)
and the Ophthalmological Department (Heads P Brændstrup and M S Norn)
The Copenhagen City Hospital Copenhagen Denmark

JUVENILE DIABETES STARTING AS FOCAL SEIZURES AND ACUTE DIABETIC CATERACT

A Case Report

INGER NØRHOLM

Introduction

Whereas diabetes in the elderly is usually of insidious onset often detected accidentally without having caused any complaints its onset in children and adolescents is frequently dramatic showing violent acute symptoms The manifestations of coma and precoma are well known In the case to be reported below the initial manifestations of juvenile diabetes were not of the usual kind – coma or precoma – but entirely different and not less dramatic

Case Report

A 20 year old man previously in good health with a family history of diabetes (maternal grandmother and maternal uncle)

The patient was admitted as an emergency case to the Department of Neurology on April 29 1968 For the past 9 days there had been twitchings of the left arm and hand increasing in frequency On the day of admission there had been episodes of generalized convulsions followed by a few minutes uncon

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sciousness The seizures were of focal nature starting in the left arm Two days before admission blurring of vision in the left eye had been noticed although previously the patient had not had any visual complaints When questioned the patient thought that maybe he had been a bit tired lately but not enough to take much notice of it He denied polydipsia and polyuria

On admission he was awake and oriented Objective examination showed a trace of oral facial palsy some uncertainty in the finger nose test and loss *of deep reflexes in the lower limbs At a few minutes interval tonic clonic* twitchings occurred in the left arm and hand In the left eye the fundus could not be seen in the ophthalmoscope

On the next day urinanalysis disclosed a hitherto unsuspected glycosuria The blood sugar in the course of the day was 342 mg/100 ml 206 mg/100 ml and 266 mg/100 ml There was mild acidosis and mild prerenal azotaemia Treatment with insulin was instituted and the final maintenance dose of in sulin was 0 7 ml protamine insulin in the morning and 0 4 ml in the evening On this treatment the blood sugar concentration was acceptable only a few g of sugar was excreted in the urine there was no acidosis and the serum crea tinine dropped to normal values viz 1 1 gm/100 ml

After the second day in hospital the patient did not exhibit any neurological abnormalities and there were no further seizures like those described above *Phenytoin medication instituted immediately after admission was discontinued* in a couple of weeks and not resumed

X rays of the skull and chest showed no abnormalities Lumbar pneumo encephalography revealed central atrophy Carotid arteriography showed a slight opacity in the right parietal region which was not however considered pathological EEG Borderline case Follow up EEG a few months later Nor mal Other findings ESR 7 mm Hb 16 8 g/100 ml W R negative B P 115/85 serum creatinine 2 5 1 6 1 1 mg/100 ml Spinal fluid normal

Ophthalmological examination two days after admission showed the visual acuity in the right eye to be *6/9 – 3 25* in the left eye *1/36 – 3 5 Slit lamp* inspection showed on the right incipient cataract on the *left a more dense* cataract Morphologically the cataract was of a peculiar nature with numerous punctate to larger plaques of sub capsular opacities interspersed by numerous vacuoles

The left side cataract nearly matured in six weeks and the right side cataract in four months In both eyes cataract discission was performed followed by extraction in the left eye Postoperative visual acuity was 6/6 with correction in both eyes Ophthalmoscopy showed no diabetic fundus changes

Twenty three months after the first symptoms the patient was re examined During the intervening period there had been no seizures or other systemic complaints Repeated *X rays of the skull showed no abnormality* EEG Borderline case – mild bilateral non specific dysrhythmia Conclusion of

neurological examination The patient has no intracranial lesion and the previous seizures must have been due to the precomatous condition The examination now revealed areflexia indicating mild diabetic polyneuropathy The patient refused to submit to further neuroradiological examinations

Discussion

That cataract is more common in diabetics than in non diabetics is well known (2 3) In a Danish material of senile cataracts 10 per cent were in diabetics Among elderly diabetics cataract occurs about 5 times more frequently than among non diabetics (9) In elderly persons however cataract is such a common occurrence that it is difficult to decide in each case the relationship between diabetes and the cataractous changes especially as cataract in elderly diabetics does not differ morphologically from cataract in others

It is different in younger people in whom cataract is rare and in whom a special type of juvenile diabetic cataract with distinct characteristics may be distinguished It is always bilateral although it may differ in maturity in the two eyes It manifests itself as dense white sub capsular opacities (the so called snowflake cataract) fine uniform needle shaped opacities and sub capsular in particular posterior vacuoles and clefts This type of cataract has been described in detail by Kirwan (6) and by O Brien & Allen (10 11) Other diabetics may exhibit a less characteristic type of cataract consisting in sub capsular opacities posterior as well as anterior (2)

The reported frequency of diabetic juvenile cataract differs within wide limits Lenticular opacities – including very small asymptomatic ones – are observed in 2–50 per cent of all juvenile diabetics (2) O Brien & Allen found 36 cases among 760 diabetics under 21 years of age (11) Most cases have been observed in older children and adolescents but the finding has been made in infants as young as 11 months (8) A characteristic feature of the snowflake cataract is that it usually occurs in poorly controlled diabetics – which applies to all O Brien & Allen s cases – and that in such instances it may mature very rapidly even more rapidly than in our patient A stormy course of a few days is on record (5 11) The great majority of the cases have occurred in persons with known diabetes of several years duration The cataract rarely gives rise to symptoms at the time when diabetes is diagnosed However Caird Pirie & Ramsell (?) have reported that of 383 new cases of diabetes under 40 years of age ? had typical snowflake cataract It has also been stated that the maturation of the cataract may be arrested or at least delayed when the diabetes is adequately treated (11) This certainly did not apply to our case where the cataract progressed inexorably in spite of insulin therapy There have been

sciousness The seizures were of focal nature starting in the left arm Two days before admission blurring of vision in the left eye had been noticed although previously the patient had not had any visual complaints When questioned *the patient thought that maybe he had been a bit tired lately* but not enough to take much notice of it He denied polydipsia and polyuria

On admission he was awake and oriented Objective examination showed a trace of oral facial palsy some uncertainty in the finger nose test and loss of deep reflexes in the lower limbs At a few minutes interval tonic clonic twitchings occurred in the left arm and hand In the left eye the fundus could not be seen in the ophthalmoscope

On the next day urinanalysis disclosed a hitherto unsuspected glycosuria The blood sugar in the course of the day was *342 mg/100* ml *206* mg/100 ml and 266 mg/100 ml There was mild acidosis and mild prerenal azotaemia Treatment with insulin was instituted and the final maintenance dose of in sulin was 0 7 ml protamine insulin in the morning and 0 4 ml in the evening On this treatment the blood sugar concentration was acceptable only a few g of sugar was excreted in the urine there was no acidosis and the serum crea tinine dropped to normal values viz 1 1 gm/100 ml

After the second day in hospital the patient did not exhibit any neurological abnormalities and there were no further seizures like those described above Phenytoin medication instituted immediately after admission was discontinued in a couple of weeks and not resumed

X rays of the skull and chest showed no abnormalities Lumbar pneumo encephalography revealed central atrophy Carotid arteriography showed a slight opacity in the right parietal region which was not however considered pathological EEG Borderline case Follow up EEG a few months later Nor mal Other findings ESR 7 mm Hb 16 8 g/100 ml W R negative B P 115/85 serum creatinine 2 5 1 6 1 1 mg/100 ml Spinal fluid normal

Ophthalmological examination two days after admission showed the visual acuity in the right eye to be 6/9 – 3 25 in the left eye 1/36 – 3 5 Slit lamp inspection showed on the right incipient cataract on the left a more dense cataract Morphologically the cataract was of a peculiar nature with numerous punctate to larger plaques of sub capsular opacities interspersed by numerous vacuoles

The left side cataract nearly matured in six weeks and the right side cataract in four months In both eyes cataract discission was performed followed by extraction in the left eye Postoperative visual acuity was 6/6 with correction in both eyes Ophthalmoscopy showed no diabetic fundus changes

Twenty three months after the first symptoms the patient was re examined During the intervening period there had been no seizures or other systemic complaints Repeated X rays of the skull showed no abnormality EEG Borderline case – mild bilateral non specific dysrhythmia Conclusion of

neurological examination The patient has no intracranial lesion and the previous seizures must have been due to the precomatous condition The examination now revealed areflexia indicating mild diabetic polyneuropathy The patient refused to submit to further neuroradiological examinations

Discussion

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cases in which pronounced changes of the lens have proved reversible disappearing entirely when the diabetes was controlled however this is exceptional (1, 4)

While *acute* diabetic cataract is a well known though uncommon manifestation *generalized* seizures do not belong to the clinical picture of coma or pre*coma* Seizures are a common complication to hypoglycaemia but are never – except for one report – reported as a complication to hyperglycaemia Of course it *cannot* be proved that our patient s seizures were in fact caused by the diabetes but it does seem extremely likely for the following reasons

In spite of careful investigations including EEG and neuroradiological examinations no other cause could be found Moreover the seizures arose in connection with the hyperglycaemia stopped entirely after sufficient insulin therapy had been instituted and have not recurred

In the literature it has been possible to find only one report on seizures complicating hyperglycaemia Maccario Messis & Vastola (6) collected 7 cases of diabetics with seizures as a manifestation of hyperglycaemia Their cases differ from ours in being elderly – in the age range 48 to 79 years whereas our patient was only 20 years of age – and in not being accompanied by ketoacidosis, whereas our patient had mild acidosis On the other hand there are many similarities One of the 7 patients had generalised convulsions but in all the others the seizures were focal The majority were unconscious during the episodes but a few had noted twitchings of the limbs initially The EEG was abnormal in all the cases but returned to normal on antidiabetic treatment to which the seizures also yielded completely whereas they had been unaffected by usual anticonvulsant medication Carotid angiography proved normal in the 4 survivors one exhibited at autopsy two small cortical infarcts of a site corresponding to the focal seizures and two exhibited entirely normal brains The survivors had various neurological symptoms during the first days after the seizures but these symptoms subsided completely and did not return

These authors felt convinced that the seizures were due to the hyperglycaemia which as already mentioned was unaccompanied by ketosis They suggest that hyperglycaemia may elicit epileptic activity in a cortex having a functional or slight structural disturbance caused by some focal lesion such as vascular insufficiency The mechanism may be imagined to be the result of the associated hyperosmolarity or a direct toxic effect

The same argumentation may be applied to our case

Summary

A 20 year old man with hitherto undetected diabetes was admitted with focal seizures for which no other explanation could be found He was not put on

anticonvulsant medication except for a very short time but the diabetes was controlled Thereafter the neurological manifestations disappeared and have not recurred during a follow up period of two years Simultaneously with the convulsive manifestations the patient developed a stormy acute diabetic cataract whose further progress could not be checked by the insulin therapy At the time of his first admission the patient had a high blood sugar concentration and acidosis but did not exhibit diabetic coma

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TRANSACTIONS OF THE DANISH OPHTHALMOLOGICAL SOCIETY 1969–1970

BY

E GOLDSCHMIDT Secretary

425th Meeting September 27 1969 in Copenhagen (Eye Department University Hospital Blegdamsvej)

P M Møller *Operation films*
(a) *Recession of eye muscles by the self edge method*
(b) *Trans conjunctival obliquotomy*

Discussion *V Clemmesen K Dreisler*

Michael Nielsen *The blood vitreous barrier*

Discussion *O A Jensen N Ehlers*

M S Norn *Dendritic keratitis A follow up study of the corneal sensibility* Publ Acta ophthal (Kbh) vol 48 1970 91 108 214–226 227–236 383–395

Discussion *J Edmund Godfred Larsen E Skeller P Kjer E Sebber V Bulow*

S Ry Andersen *On Centralisation of Radiotherapy of Retinoblastoma*
In the eastern and central states of the United States the treatment of retinoblastoma has been extensively centralized at Presbyterian Hospital New York where about 50–60 new cases are being treated every year

The chief method [1] is still enucleation of the first and radiotherapy of the second eye but occasionally also of the first All examinations are performed by Dr Ellsworth or Dr Reese always under anaesthesia The results are traced on a diagram and the treatment is in close collaboration with the radiotherapist Dr Tretter The standard treatment is high voltage X ray irradiation (betatron) in the more unfavourable cases combined with chemotherapy in the form of T E M administered intraarterially Small

tumours and recurrences are often treated by electrocoagulation Orbital exenteration is used in the event of recurrences in the optic nerve or orbit

The last analysis[2]) showed freedom from recurrence with a visual acuity exceeding 10/200 in 87-60 per cent of groups 1–4 lower for group 5 For the entire material the rate was about 50 per cent.

In Denmark the treatment is centralized in the Radium Centre for Jutland in Århus In spite of great skill and energetic efforts the results are considerably inferior to those in New York However the tumours in the Danish material are considerably larger than in the American one

The Danish results may no doubt be somewhat improved by the following measures

The ophthalmologists should follow the second eye regularly at intervals of a couple of months under anaesthesia so that radiotherapy may be instituted earlier than is now the case

The radiotherapy may be technically improved in several respects *inter alia* by using high voltage units instead of cobalt (this is already being altered) Electrocoagulation and T E M should be used more liberally

All considered however I do not believe that technical changes will afford marked improvement No doubt the decisive factor is a sufficiently large material Even the most efficient team is unable to gather sufficient experience by treating a few cases annually and definitely not experience enough to try irradiation of the first eye

At long sight I feel that the radiotherapy of retinoblastoma should be solved on a Scandinavian level As many Scandinavian countries as possible, preferably all of them should centralize the treatment in one radiotherapy department combined with an eye department Some of the follow up examinations could be carried out in the respective countries Where such centralization should be located has to be jointly decided by radiotherapists and ophthalmologists I suggest that a discussion on centralization be instituted in the Scandinavian countries

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Discussion N *Ehlers V A Jensen H H Seedorff H Ehlers P M Møller M Warburg*

Extraordinary General Assembly

Discussion and approval of the report on future structure and educational problems in Danish ophthalmology Publ Ugeskr Læg 131 1969 2004–2009

Extraordinary Meeting on October 7 1969 in Copenhagen
(Eye Department University Hospital, Blegdamsvej)

W o l f g a n g Z e m a n University of Indiana *Some problems of Spielmeyer Vogts disease*

426th Meeting, November 14 1969 in Copenhagen
(Eye Department University Hospital, Blegdamsvej)

R L G r e g o r y Edinburgh *Perceptual Implications of Recovery from Early Blindness*

R L G r e g o r y *Understanding Perception Through Illusions*

D i s c u s s i o n *H Skydsgaard M Warburg*

427th Meeting December 6 1969 in Copenhagen
(The Steno Memorial Hospital Gentofte)

N o r m a n A s h t o n London *The Pathogenesis of Diabetic Retinopathy*

428th Meeting January 30 1970 in Copenhagen
(Eye Department University Hospital Blegdamsvej)

N R o s e n b e r g *Corrosion of the Conjunctiva Complicated by Contamination by the Isotope ^{35}S*

An accident occurred in a biological institute where an isotope technician was hit in

the ocular region by the contents of a crushed ampoule. The ampoule contained the organic sulphuric compound p toluene sulphonic acid anhydride, containing the isotope ^{35}S

On contact with water the sulphonic acid anhydride is converted into sulphuric acid Immediately after the accident the patient was treated by irrigation of the eye Examination in the Eye Clinic of the University Hospital Blegdamsvej half an hour after the accident disclosed merely a superficial conjunctival corrosion which was excised

Activity measurements were instituted a few hours after the accident and showed appreciable contamination of the laboratory where it had taken place and of the technician's clothes *Less pronounced contamination was ascertained in the treatment room* of the Eye Clinic. These activity measurements were carried out by the National Health Service Laboratory for Radiation Hygiene at the Health Physiology Department *Risø*

The content of the crushed ampoule was 5 millicurie ^{35}S of which at most 2.5 millicurie can have hit the patient

In the periocular area an activity of the magnitude 2 microcurie was measured a few hours after the accident Another approx 9 microcurie was excreted in the urine during *the subsequent days*

At the primary treatment (irrigation) therefore, the contamination was estimated to have been reduced by a factor of 1000

Autoradiography of the tissue removed from the conjunctiva showed the activity to be localized to the epithelial surface

The activity in the patient's urine decreased in a few days to immeasurable values In the periocular area, on the other hand activity could be traced for weeks after the accident Attempts at accurately locating the activity showed that presumably it was in the cilia and supercilia

The measurements cannot form the basis of a calculation of the absorbed dose in particular with a view to the lens ^{35}S emits beta particles with a mean energy of 0 05 MeV which has *little tissue penetrance and it is estimated that the risk of reaching a* cataractogenic dose is negligible

With the increasing use of radioactive isotopes in industry science and clinical practice similar accidents may be expected to occur now and then. In that event radiohygienic expert assistance should be called immediately

Discussion *E Vesterdal E Gregersen P Brændstrup M Warburg H Ehlers S Ry Andersen*

J Hvidberg Hansen *Enzyme Histochemical Studies of the Iridic Pigment Epithelium*

In a series of experiments the irides of 19 rabbits were investigated for enzyme content in the pigment epithelium

This was done by the light microscopic techniques described by Burstone (1958) and by Thomas & Pearse (1961) The former method was used for studying non specific alkaline and acid phosphatase while a number of dehydrogenases were assessed *in* Henning Andersen's modification (1965) of the latter method

The dehydrogenases studied were lactic beta hydroxy butyric *succinic, isocitric and* glucose 6 phosphate dehydrogenase The three last mentioned enzymes were found to be present in a fairly small quantity in the *epithelium somewhat less than the* content in the epithelium of the ciliary body Alkaline and acid phosphatases showed a marked difference in the content *in that part of the* pigment epithelium which is situated immediately behind the sphincter where it was of approximately the same magnitude as in the ciliary body whereas in the more peripheral parts of the iris there

was a fairly low content of the named enzymes For lactic and beta hydroxy butyric dehydrogenase there was a tendency to a lower content in the juxta pupillary zone than in the peripheral area

Moreover preliminary experiments have been performed visualizing acid and alkaline phosphatases on the same type of tissue on the fine structural level by an electron microscopic technique Hugon & Borgers method was used for visualizing alkaline phosphatases (1967) and Barka s technique for the acid phosphatases (1964) Non specific alkaline phosphatases were found to be localized at the invaginations corresponding to the surface and sides of the epithelial cells and at the microvillous structures situated on the cellular surface facing the stroma This applied to the epithelial cells in the ciliary body as well as in the iris the invaginations being somewhat more scanty and scattered in the latter

It seems to be characteristic of the juxta pupillary part of the pigment epithelium that the acid phosphatases are localized to the pinocytotic vesicles while this did not apply to the ciliary body or to the epithelium on a level with the dilatator of the iris

Discussion V *Ehlers O A Jensen H Ehlers*
(The investigation will be published in Zeitschrift fur Zellforschung 1971)

K Rasmussen & A Faurbye *Follow up Study of Chlorpromazine Changes in the Lens of Long term Treated Patients*

Discussion *E Skeller V Dreyer O A Jensen S Ry Andersen*

P H Madsen *Haemorrhagic Glaucoma – Aetiology and Clinical Course*

A comparative study of heamorrhagic glaucoma in 30 diabetic and in 40 non diabetic patients was reported All patients admitted to the ophthalmological department of the Århus Municipal Hospital University of Århus during the five year period 1963–1967 were included in the study

Among the non diabetics 26 had recognized thrombosis of the central retinal vein This was found in 6 of the diabetics

Three of the non diabetics had severe arteriosclerosis or occlusion of the central retinal artery but no central vein thrombosis In 11 of the non diabetics the fundus could not be observed Retinal arteriosclerosis was found in nearly all 70 patients

The average age among the diabetics was 49 years among the non diabetics 67 years Proteinuria was found in 17 of the diabetics but in only one non diabetic

All the diabetics but one had long term diabetes 24 even proliferative retinopathy in one or both eyes

The clinical course of the haemorrhagic glaucoma was identical in patients with and without diabetes In most cases the intraocular pressure was about 45–50 mm Hg

Six diabetics and one patient with thrombosis of the central vein had bilateral haemorrhagic glaucoma whereas the glaucoma was unilateral in the remaining 63 patients

Simple glaucoma did not occur among the diabetics but was observed in 40 per cent of the non diabetics Hypotonia prior to the haemorrhagic glaucoma was noted in 12 diabetics

Rubeosis of the iris and vessels in the chamber angle are crucial features in haemorrhagic glaucoma Rubeosis was observed in 69 patients prior to or *simultaneously* with the onset of haemorrhagic glaucoma Secondary rubeosis was encountered in only one non diabetic patient Among 14 diabetics and 2 non diabetics previously examined rubeosis of the iris had been seen prior to the development of haemorrhagic glaucoma in 11 eyes for more than 12 months In 7 eyes the rubeosis remained unchanged for 2–6

years without subsequent haemorrhagic glaucoma and in 3 non glaucomatous eyes the rubeosis disappeared spontaneously

Discussion *H Skydsgaard V Dreyer P Brændstrup H Ehlers O A Jensen*

I H Madsen *Haemorrhagic Glaucoma – Treatment*

Treatment of heamorrhagic glaucoma is an unrewarding task In nearly all cases vision is lost and the only objective of the trea ment is to relieve the pain which is often very intense

/7 eyes in /0 patients were treated for haemorrhagic glaucoma during the five year period 1963–1967 at the Department of Ophthalmology Århus Municipal Hospital University of Århus In 18 of the eyes conservative treatment (pilocarpine diamox and oral glycerin) or retrobulbar injection of alcohol resulted in subsidence of pain, and further treatment was unnecessary X ray irradiation, given in three cases proved in effective Primary enucleation of the eye was performed in two cases

54 eyes were subjected to some type of operation The most common procedure was Preziosi s filtering operation with galvano-cauterization which was performed in 31 eyes at least 17 remained free of pain for from 12 months to 4 years including 8 in which the intraocular pressure returned to normal During the last 2 years cyclocryo therapy had also been used but the follow up periods were too short for a proper evaluation of the long term effect

The postoperative course did not seem to differ in diabetic and non diabetic patients

11 of the /7 eyes had to be removed

Discussion *P Svane Kn dsen* In the Eye Department, Kolding we have successfully used Vogt s cyclodiathermy electrocoagulating the ciliary body in two rows sometimes supplemented by three perforating coagulations and finished by puncture of the chamber to reduce the tension on the day of operation Since 1963 we have carried out 39 cyclod athermic procedures in 32 cases of haemorrhagic glaucoma and in 7 of secondary absolute painful glaucoma Eight of these 39 eyes have later been enucleated because of phthisis panuveitis or an incontrollable high tens on. In the remaining 31 patients we have obtained a mean tension of [illegible] mm and all eyes are reported to be painless Perusal of the case records has revealed that patients with haemorrhagic glaucoma are often in a poor general condition and a striking number have died within the first years

Cycl diathermy was recommended as a gentle operation, which preserves the eye ball in abs lute painful glaucoma

Further discussion *H Ehlers H Skydsgaard*

P M Møller & E Goldschmidt *Paresis Following Strabismus Surgery*

After obliquotomy of the inferior oblique muscle and a 4 mm retroposition of the internal rect s muscle a [illegible] year old boy developed total paralysis of the internal rectus On the f llowing day it was a certa ned by re operation that the internal rectus was *in situ* The e were no s gns of haematoma but the internal rectus remained totally paralysed for [illegible] days Thereafter its function returned in a few days and the operative r ult was sati fact ry

S ilar examples f such l ng lasting paretic states after an otherwise uncomplicated operation in the hands of a trained surgeon do not seem to have been reported previously

429th Meeting Jointly with the Ophthalmological Society of Southern Sweden February 21 1970 in Copenhagen (Eye Department University Hospital Blegdamsvej)

C E T Krakau *Photoelectric Measurements of the Pupillary Aqueous Flow*
With the aim of obtaining a less elaborate method than the photographic one for measuring the pupillary aqueous flow a photoelectric technique was tried In accordance with theoretical expectations model experiments have given very satisfactory results However the inevitable small movements of the living eye cause difficulties and give dispersion in the flow estimates Attempts to solve these problems are going on

B Ehinger *Adrenergic and Cholinergic Neurons in the Eye*
Adrenergic (sympathetic) nerve terminals in the eye were studied by the Falck Hillarp fluorescence technique The connection with cholinergic nerves was investigated *inter alia* by the methylene blue technique The sphincter as well as the dilatator pupillae muscles were found to contain adrenergic (sympathetic) *as well as* cholinergic (parasympathetic) nerve terminals By light as well as electron microscopy it was demonstrated that the terminals are situated so close together that axonal contact may easily occur This finding has been interpreted to the effect that frequently the peripheral autonomic nervous system contains a predominant type of nerve terminals and a modulating type The density of adrenergic nerves varies within wide limits between the animal species even between various monkeys and man Adrenergic terminals are abundant in ciliary processes and beneath the epithelium of the ciliary body without major species variations In the trabecular network of the chamber angle on the other hand the variations are pronounced Among primates man has very few adrenergic terminals while e g the capucine monkey (*Cebus capucinus*) has a relatively large number Like the iris muscle the ciliary muscle has a double innervation The number of terminals varies widely between the various species Man has relatively few Humans and monkeys of the old world have a thin layer of adrenergic neurons in the inner plexiform layer of the retina Monkeys of the old world have terminals throughout the inner nuclear and plexiform layers possibly in contact with photoreceptors Adrenergic cell bodies are present in the inner nuclear and inner plexiform layers and among the ganglion cells The majority of retinal adrenergic neurons contain dopamine as transmitter substance

G Stigmar *The Diagnostic Value of Adaptometric Examination in Diseases with Vitamin A Deficiency*
Preliminary data were reported from a systematic study of the light sense in diseases in which a disorder of resorption metabolism or blood transportation of vitamin A could be suspected The dark adaptation curves were determined with the Krakau Öhman apparatus With the examination procedure strictly standardized intra individual variations were found to be low thus permitting an evaluation of the effect of the therapy and the course of the disease
In vitamin A deficiencies secondary to malabsorption most cases gave a good adaptometric response on vitamin A contrary to the low or absent response which characterized the patients suffering from chronic liver diseases In one case of steatorrhoea the pathological adaptation curve was normalized by a gluten free diet
In some chronic disorders of the liver the adaptation curves often have a typical

shape The transition from the photopic to the mesopic phase of vision is delayed but the terminal threshold of li ht sense may still be normal

The specific protein, Retinol Binding Protein (RBP) which is an *essential part of the* transport mechanism for vitamin A has been determined (by Par Pettersson M D Uppsala) in these patients In some patients with hepatic cirrhosis and pathologi al dark adaptation RBP was found to be extremely low and abnormal RBP values were also found in several other cases with sub normal adaptation In summary it may be stated that a *thorough examination of the* dark adaptation is still of great value in diagnosing vitamin A deficiency As a sensitive physiological test it is a useful com plement to chemical determination of the blood vitamin A concentratio n

Discussion *H Ehlers P Brændstrup O A Jensen H Frandsen S Ry Andersen*

P M Møller & J Wegener *Measurement of Oxygen Tension in the Rabbit Interi r Chamber*

Previous investigations into the oxygen tension in the rabbit anterior chamber were reviewed The authors used a polarographic method By means of a Beckman electrode inserted by the principle of Clark into the anterior chamber the oxygen tension was measured both under standard conditions the rabbit breathing atmospheric air and under conditions at which the oxygen tension in the *inspired air* was *100 per cent* The mean value in 28 eyes was found to be 69 2 mm Hg

Discussion *J Edmund E Skeller O A Jensen* V Willumsen *H Skydsgaard C E T Krakau V Rosenberg H K Dyster Aas*

E Gregersen *Clinical Features of Secondary Exodeviations* (Publ in Strabismus 69 Transactions of The Consilium Europaeum Strabismi Studio Deditum Congress London Henry Kimpton 19 0)

Secondary exodeviation was found in 69 out of 231 successive cases of exodeviations (exophorias and exotropias) The great majority (49 out of the 69 cases) had occurred after operation for convergent strabismus The *mean follow up* period after operation is 1 years Thus the material is old and includes a number of free tenotomies which are respons ble in most cases for the postoperative insufficiency of the medial rectus found in about one third of the patients The clinical features of postoperative exotropia were reviewed It was pointed out that hy*permetropia* amblyopia and abnormal retinal cor re pondence are predominant in the material The postoperative *divergent strabismus* arise in about two thirds of the cases immediately or very soon after the operation for *convergent strabismus* whereas in about one third it was a very late occurrence, on the average 13 years after the *operation for* convergent strabismus

It was concluded that caution must be displayed and *under correction* used in operat ing for non accommodat ve convergent strabismus with hypermetropia and ambl*yopia* Postoperative *insufficiency* of the medial rectus must be avoided and free tenotomy must be c nsidered ophthalmological history

Discu si n The devel pment of the secondary (*postoperative*) divergence in the pres ent material is presumably due chiefly to the follow ng factors (1) The *postoperative insufficiency* of the rectus med alis (observed in one third of the cases) ( ) Poss bly gradually decreasing *accommodation* and convergence impulses (3) The amblyopia and the abnormal retinal corre pondence wh ch *makes the* resting or sleeping pos tion of the eyes which is generally divergent predominant and *decisive to their* pos tion Early *primary* operati n f r convergent strab smus i e around the age of 1 or 2 years presumably entails a larger *number* of re operations than primary operation around the age of 3–5 years

Discussion E Goldschmidt b Bengtsson H Ehlers G Stigmar A Drenler P Brændstrup

H Bynke & O Wiebert *Ocular Hypotension in Pregnancy* (University Eye Clinic Lund Sweden)

Ocular hypotension may occur in pregnancy (1) For example Dominguez stated that a pressure *below 7 mm Hg may indicate pregnancy (2)*

Two *young women with ocular hypotension* were *treated with abortion* because of imminent blindness The *first one aged 16* was in *the third month of pregnancy* the second one aged 20 in the sixth month *Both pregnancies* were *normal* and there were no signs indicating diabetes or exogenous intoxication Both patients had binocular changes consisting of uveitis *choked discs* and retinal oedema Their ocular pressures were between 3 and 7 mm Hg *In the first* patient who was also treated by steroid medication the pressure returned to normal within 3 weeks after the abortion and the inflammatory and exudative changes gradually subsided The final visual acuity was 0 9 R E and finger *counting 1 m* L E In the second case there has been major improvement 3 weeks after the abortion i e at present The visual acuity is almost normal in both eyes

The mechanisms were *obscure* However it seems reasonable to assume that the choked discs and the retinal oedema were caused by the hypotension which was more excessive than can be accounted *for by the uveitis*

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2 Dominguez W N Oftalmotono en obstetricia y ginecologia Semana med 1951 Ref *Zentr* bl Ophth 56 249 1951/52

J Edmund & S K y Andersen *Pathogenesis of Retinal Detachment*

Retinal detachment may occur as a *result of e g* malformations severe trauma *ocular infections* or ocular *tumours Otherwise* retinal detachment presumably occurs *only* when *predisposing factors are present in the retina* choroid as well as vitreous The most important predisposing factors are lattice degeneration peripheral chorioretinal degeneration peripheral cystic degeneration and vitreous degeneration with liquefaction and syneresis All these factors are observed earlier and more marked in myopes *If they are* present a sudden movement of the eye or an indirect trauma may give rise to traction on the retina especially close to vitreo retinal adhesions resulting in a *tear* Tears are often observed without detachment and there are many findings which indicate that the French school is right in attaching great importance to transudate from the choroid However numerous factors still remain unelucidated *Norton* Machemer & *Kroll's* experimental studies producing artificial detachment in monkeys *have confirmed the clinical experience that a flat detachment* causes far less severe degenerative *changes* of the entire *inner retinal layer than* does a large detachment These experiments indicate that the retinal pigment epithelium and the choriocapillaris play a certain role in the metabolism of the entire retina The outer segments and the lameller inclusion bodies in the pigment epithelium degenerate very early (as in vitamin A deficiency) but considerable regeneration must take place if the detachment becomes re attached both experimentally and in man It is possible that a *flat detachment* is in fact no detachment at all but oedema between the stretched outer segments *It was* also suggested that the elongated *outer* segments in these cases *might be* partially due to accumulation of segments *the oedema preventing the pigment epithelium from* absorbing (*phagocytizing*) the lamellae *of the outer segments* as it normally does This

can only be decided by electron microscopy If it is correct the action of light as well as of vitamin A may possibly harm a detached retina by stimulating the production of lamellae.

This paper has been previously published in part in Rosengren B (editor) Retinal Detachment Surgery Almquist & Wiksell Gothenburg 1966 (chapter IV pp 29–44)

430th Meeting April 4 1970 in Copenhagen
(State Institute for the Blind and Weaksighted)

B Rosengren *Electrophysiological Orientation Devices for the Blind Experi ns Using the Tip of the Tongue as Receptor*

The most widely used orientation apparatus for the blind is the white stick Through the s gnals transmitted to the carrier of the stick through deep sens bility the blind person gains a punctate impression of his environment The blind person who picks his way with the stick may be likened to a person who has only a minimal visual field remnant

To obtain a more reliable orientation ability information has to be received from d fferent parts of the visual field The more information that can be procured in this way the cl ser we can approach the impression of the surroundings obtainable through indirect vision

The Polish ophthalmologist Starkiewicz has designed a camera in which the film is rer laced by a m saic of photo elements Each element is connected by a flex to a vi brat ng element A number of such vibrating elements are fixed in a position which makes it possible f r the tact le receptors in the forehead to produce sensations that may aff rd an mpress on of the surroundings Similar experiments using the dorsal skin and a larger number of elements have been performed by Bach y Rita in U S A

Recently Grindley & Lewis have performed experiments placing electrodes intra cranially over the visual cortex and inducing sensations direct from the visual cortex The test ng d ne o far has proved that this is possible but the risks involved by this stimulat on restrict the pcss b lities of its further development And indeed it is diffi cult t imag ne this method elaborated with a large number of elements

At present the utilization of the tactile sense appears to be the only possibility On this bas s, the author n c llab o ation with Professor Wallmark and Mr Carlstedt M S (Eng) f Chalmers Technical College Gothenburg has tested a stimulation based upon the high ens t vity f the tip of the tongue where tactile elements are even d n er than in the finger tips. The idea is that w th the t p of the tongue the subject sh ld explore a large number of elements contained in a plate in the palate.

451st Meeting May 2 and 3 1970 in Arhus (Scanticon)

Subject *Metabolic Ocular Chang s*
Invited experts *J Melchior M D and N J Brandt M D*

H W Iarsen *Modern Treatment of Diabetic Retinopathy*

After briefly reviewing previous attempts at treating diabetic retinopathy the author gave a more detailed account of this treatment using photocoagulation and hypophysec tomy

It was concluded that the treatment of diabetic retinopathy was far too often un satisfactory due not least to the fact that many patients are referred too late

In the author s experience photocoagulation seems able in many cases to delay the further progress of the retinopathy or even to arrest it for a long period Photocoagula tion is preferable to hypophysectomy in the early stages of proliferative retinopathy

Although it is a palliative procedure photocoagulation must be considered the most gentle method available so far and the one that best preserves vision Although we do not yet know the long term prognosis this treatment should be continued until better pos ibilities become available

Only by a more profound underst nding of the pathogenesis of diabetic angiopathy can we arrive at a preventive and effective treatment of the retinopathy

P H Madsen *Ocular Findings in Proliferative Diabetic Retinopathy*

During the period 1963–1968 the author examined 123 diabetics with proliferative retinopathy at the Eye Department of the Arhus Municipal Hospital University of Arhus 61 males and 62 females 69 per cent of the patients were under 50 years of age The average duration of diabetes was 22 years and in 61 per cent the onset of diabetes had been before the age of 20 The great majority were on insulin 60 per cent had proteinuria 25 per cent elevated serum creatinine and 23 per cent a diastolic blood pressure exceeding 100 mm Hg

In 43 per cent of the eyes the visual acuity was $\geq 0\ 33$ in 65 per cent $\geq 0\ 33$ in one or both eyes while 20 per cent had a visual acuity $< 0\ 1$ in both eyes

70 per cent of the patients had lenticular opacities of different degrees most often there was a posterior cortical cataract and snowflake like opacities

Iridic rubeosis was observed in 96 eyes of 63 patients In several of the eyes this con dition had persisted for several years Only 21 of the eyes developed haemorrhagic glaucoma and in 15 eyes the rubeosis disappeared entirely

The intraocular pressure was on the whole low in patients with proliferative retino pathy lowest in eyes with pronounced proliferations

Common diabetic retinopathy was present in most of the eyes Proliferative retino pathy was observed in all degrees of severity from small vascular new formations to severe connective tissue proliferations Detachment of the vitreous was observed in 105 out of 189 eyes and retinal detachment in 52 In 17 of these eyes a few venous coils were seen attached to the posterior vitreous membrane Several cases gave an impres sion of a considerable traction on the proliferations and retina

Vitreous detachment occurred with particular frequency in eyes with connective tissue proliferations In 65 eyes there were retrovitreous haemorrhages and in 19 intra vitreous

Photographs of the various fundal changes were demonstrated

S E Simonsen *ERG in Diabetic Retinopathy Prognostic Use*

Discussion on the above papers: *J. Brandstrup, H. Ehlers (vide infra), F. Gregersen, O. A. Jensen, H. Skydsgaard, J. Edmund, N. Williamsen, T. Bertelsen, E. Goldschmidt, S. Ry Andersen, K. Deutler, J. Westerlund.*

H. Ehlers: Had admired Hans Walther Larsen's skillful technique in the photocoagulations and hoped that this treatment might be beneficial in this dreaded retinopathy. At any rate photocoagulation is a far more limited procedure than hypophysectomy but is nevertheless a mutilation and does not repair the damage done in the retina. Besides we do not know whether the vascular proliferations are the primary factor in the genesis of the retinopathy or merely a striking reaction to another process – perhaps in the vitreous, and possibly of immunological nature. As a rule several years elapse between the diagnosis of diabetes and the onset of retinopathy. We must utilize this long period and institute prophylaxis. It also seems beyond doubt that according to the experience made in the Steno Memorial Hospital the severe cases of diabetic retinopathy have become more uncommon during the past decade, presumably because of increased medical supervision of the patients' condition. The question is whether local ocular factors are at play apart from the systemic ones. This is indicated by the fact that the two eyes in the same diabetic may at times behave differently. There is also reason to point out what has been my experience in the course of the years and which has now been confirmed from several quarters, viz. that myopic diabetics have milder ocular complications. We do not know why. It might be imagined to be due to less accommodation strain and a possible protection by the glasses etc. Protecting the eyes from light and visual strain which was so important in the earlier ophthalmological literature on retinopathy, has been lightly treated by modern ophthalmologists, but perhaps not rightly. It must be borne in mind that the retinal metabolism is a carbohydrate metabolism.

It is not my impression that any relationship exists between the transient changes in refraction and a subsequent development of retinopathy. On the contrary, I have known patients who started having severe refractory changes, but who have not yet developed retinopathy 20 years later. Indeed retinopathy occurs in far from all diabetics.

M. Warburg: *A Review of Diagnostic Possibilities in Fetal Ocular Diseases of the Eye.*

E. Godtfredsen: *New Aspects of the Classification and Pathogenesis of Lipidoses with Neuro-ophthalmological Manifestations.* (Publ. in extenso in Acta Neurologica Scand. 1970)

Lipidoses are rare diseases involving severe symptoms from the eyes, central nervous system and parenchymal organs. The ocular symptoms may be early and frequent, often so typical that the ophthalmologist may suggest or make the diagnosis. Thus the ophthalmological interest in these diseases is understandable. After having been known for almost 100 years the lipidoses have been recognized most recently as congenital enzyme defects: inborn errors of metabolism. The presuppositions are partly recent activity in the biological sector – in particular within biochemistry, molecular biology (the DNA molecule) and genetics – and partly the re-discovery of Archibald Garrod's pioneer study on inborn errors of metabolism from 1908 which after about 40 years oblivion has become topical and now comprises about 100 diseases, many of which including the lipidoses – involve characteristic ocular manifestations.

O. A. Jensen & H. W. Larsen: *The Clinical and Histopathological Appearances of Some Lipidoses with Ocular Manifestation.*

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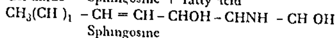
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The lipidoses demonstrated are listed in Fig 1 Gaucher s disease which does not involve retinal changes was excluded from the review Each disease was demonstrated by pictures of the fundus and by specimens studied histologically as well as histochemically It was pointed out that from a biochemical point of view Spielmeyer Vogts disease is outside the group

Fig 1

Cerebral and retinal lipid storage disease (neurolipidosis) (simplified)

Name of the disease	Stored lipid	Composition of lipid
Mb Gaucher	Cerebroside	Ceramide + hexose
Mb *Greenfield* (metachromatic leucodystrophy)	Sulphatides	Ceramide + hexose + sulphate
Mb Fabry (angiokeratoma *corporis diffusum*)	Ceramide trihexoside	Ceramide + glucose + galactose + galactose
Mb Tay Sachs (infantile amaurotic family idiocy)	Ganglioside	Ceramide + glucose + galactose + NA galactosamine + NANA
Mb Niemann Pick	Sphingomyelin	Ceramide + phosphoric acid + choline
Mb Spielmeyer Vogt (juvenile amaurotic family idiocy)	Lipofuscin?	Oxidized unsaturated fats and oils?


Ceramide = Sphingosine + fatty acid

$CH_3(CH\ )_1 - CH = CH - CHOH - CHNH - CH\ OH$

Sphingosine

O A Jensen *Ocular Histopathology in Cargoylism*

The ocular changes in gargoylism were reviewed in general In particular the author demonstrated a case of mucopolysaccharidosis III (Sanfilippo s syndrome) The histological and histochemical findings in this case were demonstrated and the correlation between the histochemical findings and the biochemical defect was discussed

The material will be published *in extenso* in Acta pathol microbiol scand

Discussion on the above papers V *J Brandt J Melchior H Skydsgaard E Godtfredsen (vide infra)*

E Godtfredsen Among the approx 100 known metabolic diseases due to congenital enzyme defects ocular signs occur with a high frequency in about 20 per cent or exactly as in congenital diseases in general Ocular manifestations are seen in the refractive media (cornea+lens) and the perception apparatus (cf Table) The frequency and specificity vary from the modest uncharacteristic to the frequent and pathognomonic e g Kayser Fleischer s ring and sunflower cataract in Wilson s disease the lens ectopia in homocystinuria and the cherry red patch in Tay Sachs The practical clinical in

terest displayed by the ophthalmologist and his possibility of arriving at the aetiological diagnosis are well motivated

Table

Eye sign in metabolic diseases		Cornea	Lens	Retina
Aminoacidurias	Cystinosis Fanconi	+		
	Homocystinuria		Ectopia	
	Lowe oculo cerebro renal		+	
Sugar metabol sm	Galactosaemia		+	
	Glycogen deposit	+	+	
	Hurler – Gargoylism	+		
	Diabetes mellitus		+	+
L pidosis	Tay – Sachs			+
	Niemann – Pick			+
	Fabry	+	+	
	Refsum		+	+
Various causes	Wilson hepato lentic	+	+	
	? dystrophia myotonica	+	+	+

E Goldschmidt & G Pallisgaard *The Oculo cerebro renal Syndrome of Lowe in Four Generations of One Family* Publ Acta paediat (Uppsala) 19((

Discussion V *J Brandt J Melchior S Ry Andersen A Other*

F Kruse *Ocula Changes in Homocystinuria* Publ Acta ophthal (Kbh)

S Kessing *I fantile Cystinosis*

Cystinos s is a rare disease transmitted by *autosomal recessive inheritance* showing typical crystals of cyst ne in the cornea conjunctiva uvea and bone marrow as well as in phagocytes in numerous organs

Cyst nosis o curs in an nfantile mal gnant form which usually leads to death before the age of 10 and in an adult form *which is benign* without subjective symptoms The poor prognos s of infantile cystinosis is due to a renal lesion of the Fanconi type causing enal rickets The renal lesion is not a link in adult cystinosis in which incidentally th *above mentioned* depos ts of cyst ne are also present

The underlying biochemical defect has *not* yet been discovered but recent investiga t ns indicate that it is located in the organelles of the individual cells accumulations of cyst ne crystals having been found n lysosomes in histiocytes and fibroblasts from the *conjunctiva of child* en and adults with cystinos s

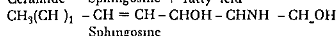
Typical infantile cystinosis *in 2 brothers was reported* The diagnosis was based upon

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TRANSACTIONS OF THE OPHTHALMOLOGICAL SOCIETY OF FINLAND MEETINGS 251–262

Meeting 251 January 23 1967

Tauno Larmi *The need of beds for the treatment of eye diseases*

Matti Kaivonen *The anatomy of fascia and strabismus operation*

Matti Kaivonen *The anatomy of fascia bulbi and strabismus operation*
Operation for strabismus is an easy and simple operative procedure The complications are usually not dangerous but sometimes very troublesome Most of the complications occur in the healing of the conjunctival incision.

The conjunctiva is opened in the conventional manner 6–10 mm from the limbus behind the insertion of the rectus muscle to be operated on The conjunctiva the muscle sheath the intermuscular membrane and Tenon's capsule are attached to one another at this site by loose connective tissue and easily separate into different layers during the operation When the incision is closed either by interrupted or continuous sutures the layers may sometimes overlap and then granulation will grow in the scar and must be removed by cauterisation or excision The ensuing scar is fairly prominent On the other hand if the fascial layer is not tightly closed the conjunctiva will be cicatrised right to the surface of the sclera The scar is also visible and often constricting In addition if new vessels grow through the opening in the fascial layer from the muscle insertion to the conjunctiva the scar will remain hypermic for a long time The conventional incision severs relatively large conjunctival vessels and the new vessels in the scar are fairly large even in the conjunctiva itself and visible for a long time Most of these complications can naturally be avoided by closing the incision with extreme care but even then complications may occur occasionally from premature loosening of the sutures

It has been our practice in Jyvaskyla since the beginning of 1964 to make the conjunctival incision in the limbus in surgery for strabismus In our experience the wound then heals more quickly and better and the ensuing scar is practically invisible The conjunctiva is incised in the limbus at the muscle to be operated on for a length of 3–4 hours At both ends of the limbal incision radial incisions 3–4 mm in length are made perpendicularly to the limbus As the conjunctiva and the fascia are fused into a single layer ca [illegible] mm from the limbus limbal incision gives direct access to Tenon's

microscopic examination of unstained conjunctival biopsies by the method of Brændstrup Renal biopsies had suggested the diagnosis nephronophthisis The peripheral pigmented retinopathy said to be the first sign of infantile cystinosis could not be definitely demonstrated

A diagnosis of cystinosis should be called to mind by the named ocular findings and may be confirmed by examination of the bone marrow for crystals and determination of the cystine content in peripheral leukocytes

Discussion on the last two papers *M Warburg N J Brandt J Melchior N Ehlers S Ry Andersen P M Moller F Gregersen O A Jensen*

N Tygstrup S Keiding & I Mellemgaard *Cataractogenic Effect of Combined Galactose ethanol Administration in Rats* Publ Acta ophthal (Kbh)

Discussion *N J Brandt H H Seedorff E Godtfredsen H Ehlers O A Jensen*

L Østerby *Ocular Changes in Wilson s Disease*

After a brief review of Wilson s disease a family of 6 siblings was demonstrated 7 or perhaps 3 affected It is important to demonstrate Kaiser Fleischer s ring which is pathognomonic of the disease but which is present in only 60–90 per cent of the cases

Discussion *N J Brandt O A Jensen E Godtfredsen S Ry Andersen*

N Ehlers & T Kruse *Corneal and Conjunctival Changes in Chronic Renal Failure* Publ Acta ophthal (Kbh)

Discussion *O Hartkopp N Rosenberg S Ry Andersen O A Jensen V Wildlumsen E Godtfredsen A Other J Melchior N J Brandt*

General Assembly on May 2 1970
(Scanticon near Århus)

Chairman K Rasmussen
President s and treasurer s reports
Election of president Jens Edmund was elected and expressed thanks to the retiring president S Ky Andersen The Committee now consists of Jens Edmund (President) Mette Warburg (Vice President) E Goldschmidt (Secretary)
Report from the Committee for the Prevention of Blindness Election of members E Gregersen P M Moller and S Ry Andersen
Discussion on postgraduate training

Yrjo Aantaa *Contact lenses and aphakia*
Optician Hans Cenz (Jena) *Binocular glasses*

Veikko Tommila *Use of prisms in the diagnosis and treatment of strabismus*

Valter Elenius *Absorption glasses*
Master optician Pauli Matikainen *Fitting of spectacle frames*
Master optician Eero Lång *Placing eyeglasses in position*

Matti Koskenoja *Unbreakable glasses*

Henrik Forsius *Correction of aphakia with spectacles*

The drawbacks of strong plus lenses are discussed

(1) When vertex distance increases the dioptric power and magnification of the glasses grow Subjects with high hyperopia should be operated only if necessary because a distant correction of 15-17 D causes very great difficulties Vertex distance is greater on the edge of the glasses and this increases the errors that appear in the periphery of the lens

(2) When reading a cataract lens causes a high degree of astigmatism of an oblique beam of rays even if they are normally tilted Under correction of inverse astigmatism for reading glasses is therefore recommended.

(3) Prismatic effect makes straight lines appear curved.

(4) Glasses magnify The object moves in the opposite direction when the patient turns his head. He may judge the position of objects as too close and too peripheral A ring scotoma arises at the edge of the glasses In writing the prescription lens errors must be considered and for skiascopy the patient must look at the examination light or immediately above it as close to the optic axis of the glasses as glass reflexes permit

If the patient already has cataract glasses he may keep them on during the examination The additional correction required by the change in refraction must be mentioned in the prescription so that the optician can grind the lenses to fit these frames

The patient must be advised to ask his optician for small diameter frames with interchangeable bridges so that his glasses weigh as little as possible and cause a minimum of disfigurement

Bifocal lenses are recommended only for patients requiring weak aphakic correction who have good vision, a weak add and a small round pupil

References

Benton C. D & Welsh R C Spectacles for aphakia C Thomas Illinois U S A 1966

Yrjo Aantaa *Contact lenses and aphakia*

A review of the benefits and problems in fitting aphakic patients with contact lenses The optical advantages of contact lenses over spectacles in aphakia cases were described with the help of figures Types of contact lenses power measurements and some of the main problems in fitting aphakic patients with contact lenses were discussed Reference was made to several authors (Joseph M Dixon Louis J Girard Georg Nissel Kenneth N Ogle Montague Ruben, Robert L Ullen Robert C. Walsh and others) papers and personal communications

A few examples were given of the author s own contact lens practice

M Koskenoja *Unbreakable glasses*

Eyeglasses made or ordinary crown glass have been compared with a car with no safety belt Both are good servants but in the event of an accident may cause their owner damage that could have been avoided with the use of ordinary safety devices

space between the fascia and the sclera By dissecting backwards along it the flap formed by fascia and the conjunctiva is easily detached in one layer from the sclera to behind the muscle insertion The strabismus hook is easily placed behind the muscle, and the dissection of the muscle is continued in the usual way Exposure of the whol operative area is extremely good In recession operations we usually also insert the sutures in the sclera at the measured site of the new insertion along the edges of the muscle before the muscle is severed In this way the direction of the new attachment will be absolutely correct After tying the muscle sutures the conjunctiva is simply closed with two sutures placed in the limbus in each corner of the conjunctival flap no other sutures are necessary If thin virgin silk is used the sutures are placed very superficially and pulled tight they come out spontaneously within a week and need not be removed The flap adheres rapidly throughout its surface to the scleral surface and retraction need not be feared

The incision appears to be very extensive but compared with the conventional incision it definitely heals better and quicker This is obviously due to several factors. At the limbus the fascia and the conjunctiva are fused in a single layer and no fascial prolapse can consequently ensue The edges of the incision assume the correct positioning almost by themselves although the wound is not closed tightly with many sutures The limbus is heavily vascularised but the vessels are all very small chiefly capillaries Hemorrhage from the incision is thus very slight but tissue nutrition is good and the new vessels in the scar are also very small and not unpleasantly prominent An intact fascial layer through which no vessels grow on the conjunctiva is left between the conjunctiva and the muscle insertion As the surface of the conjunctiva in the region over the muscle insertion is intact and smooth and the sutures are virgin silk the patient can open his eye without difficulty on the first postoperative day and after a week the eye is generally white and uncongested After a month the scar is only a thin white line in the limbus difficult to discern

We have also used a similar incision in surgery for the retinal detachment It is possible to incise the conjunctiva e g in cerclage operation around the limbus as a whole and two short radial incisions are made on opposing sides Exposure is extremely good and the wound is very simple to close again only two sutures placed in the limbus at the corners of the radial incisions are needed

A total of 590 operations for strabismus and 38 operations for retinal detachment have been performed in Jyvaskyla since 1964 through limbal incision In not a single case was any complication encountered in the healing of the wound

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Meeting 252 April 22 1967

Symposium on the subject The Ophthalmologists's Practical Optics April 21-22 1967 at the Institute of Occupational Health Helsinki

Hannu Voipio *Sources of error in the determination of refraction*

Martti Katavisto *Aniseikonia*

Henrik Forsius *Correction of aphakia with spectacles*

Hannu Voipio Lauri Kiianmies (1895–1967) In Memoriam

Arvo Oksala & Lotta Salminen *Enucleations at the Ophthalmic Department of the University Central Hospital in Turku in the years 1946–1966*

Terttu Karo & Valter Elenius *Changes in the refractive power of the cornea after cataract extraction*

Valter Elenius *Acquired colour sense disturbances (Farnsworth's tests 100 – hue and Panel D 15)*

A Oksala & L. Salminen *Enucleations at the Ophthalmic Department of the University Central Hospital in Turku in the years 1946–1966*

SUMMARY

The number and the indications of enucleations performed in 1946–1966 at the Ophthalmic Department of the University Central Hospital in Turku were surveyed In 1946–1963 enucleation was performed in 3 3–4 2 per cent of the patients whereas in 1964–1966 the percentage was 1 7 In 1964 the number of beds at the department increased nearly twofold Injuries were the most common cause of enucleation showing only minor variation (50–66 per cent) in the whole series 253 eyes were enucleated from males and 44 eyes from females Injuries were commonest in the males of 21–60 years and in females of 61–80 years of age Enucleations caused by tumours varied from 8 to 27 per cent 59 of the 76 tumours were uveal melanomes The proportion of absolute glaucomas was slightly lower in 1964–66 In females this was a commoner cause of enucleation than in males

Antibiotics and cortisone which in many infections and postoperative conditions are very effective have not in this material diminished the necessity for enucleations

Terttu Karo & Valter Elenius *Changes in the refractive power of the cornea after cataract extraction*

SUMMARY

Refract ve power of the cornea has been examined after intracapsular extraction of senile cataract The corneal section was performed with Graefe knife and five virgin silk corneo scleral apposition sutures were used Sutures were left unremoved for at least one month

Of 40 eyes showing astigmatism with the rule at ten days after operation 34 showed astigmatism against the rule three months after operation while in 6 eyes astigmatism

To get an idea of the role played by eyeglass fragments in serious eye accidents I went through the case reports of all the patients under treatment at the Department of Ophthalmology Central Hospital of Central Finland in 1962 1966 for eye accidents (Table) The majority of these injuries could naturally have been avoided by the use of protective glass and the five perforating injuries due to fragments of the wearers own glasses seemed to be especially futile as effective shock proof safety glass are available at a reasonable price

Safety glass materials are of three types firstly laminated glass like that used e g in car windscreens and known by the trade name triplex secondly heat tempered glass which corresponds to the Sekurit glass used in car windscreens and thirdly transparent plastic materials Laminated glass has several disadvantages and is little used today Of the plastic substances allyldiglycolcarbonate CR 39 has proved to be by far the best The translucency of this substance is slightly better than that of glass the index of refraction is almost the same as that of crown glass It tolerates all the usual solvents bases and acids and very high temperatures The surface of CR 39 can be made relatively hard a decisive advantage compared with other plastic materials The greatest advantage of plastic lenses is their lightness they weigh only approximately half of the corresponding weight of glass lens The biggest drawback of plastic lenses is the greater risk of scratching although the difference has decreased considerably in recent years Owing to different heat conductivity properties a plastic lens does not frost over as easily as a glass lens

Both thick lenses made of CR 39 and thick heat tempered glasses can stand impacts of relatively slow speed about 5–10 m/sec (which corresponds to the usual impact speed *in accidents) and the durability of both is quite adequate in this respect* On the other hand CR 39 gives distinctly better protection than heat tempered glass against very small fragments travelling at very high velocities in the range 100–500 m sec Moreover welding sparks do not burn plastic lens as they do glass

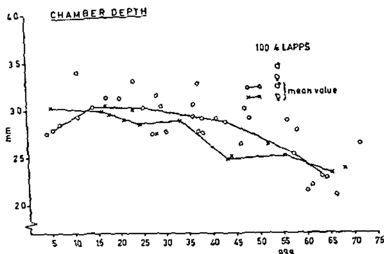
In addition to the material of which they are made the impact resistance of lenses is affected by their shape minus glasses are broken more readily than plus glasses cylinder glasses are likewise broken more easily than spherical glasses and strong minus cylinders in particular are easily broken

If the foreign body does not have very high energy what usually happens is that the foreign body that breaks the glass loses its energy on impact with the lens and the real damage is then caused by glass fragments Very dangerous sharp needle like fragments splinter off from laminated glass and ordinary crown glass and are very liable to penetrate the eyes The fragments of heat tempered glass and *CR 39 are of* fairly harmless shape

Ordinary spectacles can also be made of shock proof materials without causing the wearer any inconvenience but the purchase price is somewhat higher These glasses should therefore be more widely prescribed especially when the subject wears glasses permanently It is particularly important to make it a habit with children adolescents sportsmen and persons employed in jobs where accidents are likely to occur Very good experience *has been gained from the use of shock proof* glasses in combating industrial accidents

Eye accidents treated at the Department of Ophthalmology Centre Hospital of Central Finland in 1962–1966

Injuries penetrating the eyeball	115
– The penetrating object a fragment of the wearer s own glasses	[illegible]
Other injuries to the eye and palpebra	62
Total	37[illegible]



Figs 1–9
The depth of the anterior chamber in 156 Skolts was measured with a Goldmann anterior chamber depth gauge (Haag Streit) The anterior chamber depth is lowered with age There is no distinct difference between women and m n Interindividual variation is considerable. No noteworthy differences were established in the depth of the anterior chamber between Skolts and Fisher Lapps

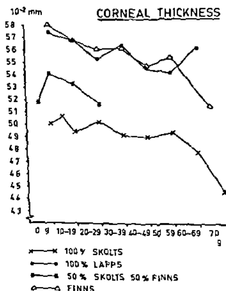


Fig 3
Corneal th ckness measured with Goldmann s (Haag Streit) device The cornea of the Skolts is an average of 0 07 mm thinner than that of the Fisher Lapps and Finns The corneal thickness of the half breed Skolts is between these two groups

with the rule persisted. In 22 eyes astigmatism against the rule was observed both at ten days and three months after operation.

Within the time from the end of the third to the end of the sixth postoperative month the average astigmatism (27 eyes) was reduced from 3.1 D ($s = \pm 1.6$ D) to 2.7 D ($s = \pm 1.4$ D) and the average direction of the axis changed less than one degree.

At the tenth postoperative day the average direction of the axis of the weakest refractive power (62 eyes) was 90.2° ($s = \pm 61.1°$) and at the end of the third postoperative month 88.3° ($s = \pm 26.2°$) respectively. In 31 right eyes the average direction of the axis (three months after operation) was 93.2° ($s = \pm 31.5°$) and in 31 left eyes 83.4° ($s = \pm 23.7°$) respectively.

Meeting 254 December 1967

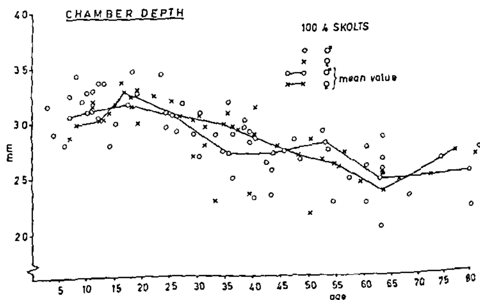
Valter Elenius: *The Nobel Prize for medicine and physiology.*

Henrik Forsius, A. W. Eriksson & H. Luukka: *Ophthalmogenetic studies on the Skolt Lapps.*

Ulf Krause & Henrik Forsius: *Routine use of the surgical microscope.*

H. Forsius, H. Luukka & A. W. Eriksson: *Ophthalmogenetic studies on the Skolt Lapps.*

Aided by the World Health Organisation and the International Biological Programme studies on Skolt Lapps were conducted in 1966–1967 in the eastern parts of Inari, northern Finnish Lapland. Scientists from Sweden, Norway and Denmark and



morning After the blood samples were taken the subjects were fed and then passed round the different investigation groups

At the ophthalmological examinations a programme of ocular refraction and other routine studies were performed The radius width and thickness of the cornea were measured and a note was made of the occurrence of arcus senilis and embryotoxon corneae Special attention was paid to the colour of the iris and the pigmentation of the eye, which was studied both by diascleral fluoroscopy and by assessing the degree of pigmentation of the fundus from the choroid and retina

Colour sense was studied with pseudochromatic tables HRR, Bostrom Kugelberg I and IIB Ishihara and Kalmus tritanopia plate Farnsworth 15 test and Schmid Hensch anomaloscopy Ten of the 214 male Skolts at Sevettijarvi and Nellim were deuteranomal and two were protanomal i e 5 6 per cent Five of the colour blind Skolts were brothers

The depth of the anterior chamber was measured in the Skolt and Fisher Lapp populations of Nellim in 1967 No differences were established between them (Figs 1–?)

The corneal thickness of the Skolts was an average of about 0 07 mm thinner than that of the Fisher Lapps and Finns (Fig 3) The corneal thickness of the 69 persons with one Skolt and one Finnish parent was between these groups (Forsius H Luukka H Fellman J Eriksson A W Bull Europ Soc hum Genet 1967 1 81–83)

The average corneal power of the Skolts was high r than that of the Fisher Lapps

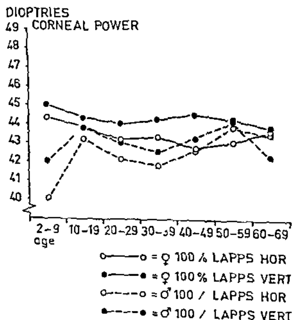


Fig 5

Corneal power of 37 male and 43 female Fisher Lapps The mean values for the males are 4? 63 D for the right eye and 4? 69 *for the left eye*. The corresponding mean values for the females are 43 44 and 43.55 A comparison with Fig 4 shows that on the average the Skolts have a higher corneal power than the Fisher Lapps

also from Germany and Belgium participated in our expedition The purpose of the research project was to study the isolated Skolt Lapps in their entirety and on a very broad basis The main aspect of the studies was ophthalmogenetic but the Skolt Lapps were also studied on the points of health anthropology pediatrics and child psychiatry A dentist performed roentgenologic examinations of the dentition and made plaster impressions of the bite Some aspects of the social history of the Skolt Lapps were also studied for registration of the exterior characteristics etc About 15 standardised photographs were taken of each subject Both eyes were photographed with a Zeiss iris camera Two black and white exposures were made of the fundus of both eyes using a Zeiss fundus camera

Routine health examinations were performed Blood samples were taken for determination of blood and serum groups and qualitative red cell enzymes In 1967 biochemical studies were performed in a field laboratory Among other things over ten red cell enzymes were studied quantitatively

The investigations were carried out in 1966 at the elementary shool of Sevettijarvi where 343 Skolt Lapps were examined They accounted for about 95 per cent of the total Skolt Lapp population resident at Sevettijarvi In summer 1967 the elementary school at Nellim was the base and 151 pure Skolts 97 half breed Skolts and 95 Lapps were examined About 10-20 subjects were asked to come to the station fasting in the

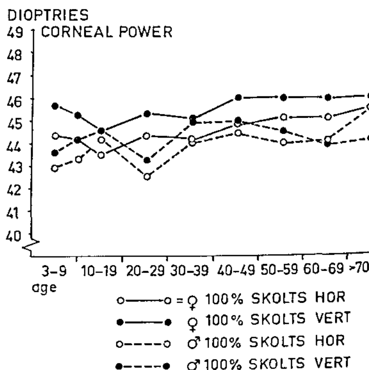


Fig 4

Corneal power measured with a Haag Streit keratometer in 68 Skolt males and 76 Skolt females in relation to age The mean values for the males are 43 87 D for the right eye and 44 04 D for the left The corresponding mean values for the females are 44 56 D and 44 69 D

The *diseased* came from 12 families which were divided into two groups (groups A and B) according to the character of the disease and the family relations of the pa tients

Among others the following results were obtained

(1) The hyalin containing reticular formation in the cornea is not a true disease but a sequela, a *scar*

(2) The actual disease involved is a *metabolic disorder*

(3) In group A the metabolic disorder is manifested as acute attacks in which poly gonal *crystals* appear transiently in the cornea, aqueous humour and possibly also in the bulbar conjunctiva There is concurrently a state of severe irritation and pain in the eye The crystals *resemble the cystine crystals in cystinosis*

(4) The metabolic disorder occurs in the *nervous system* This view is based on the observation that one patient of group A during corresponding acute attacks developed *in addition to* relatively mild *corneal dystrophy* also *bilateral atrophy of the optic* nerve. This opinion is substantiated by the results of Vrabec s neurohistologic studies in 1957

(5) It is very possible that *many diseases also when there are no acute attacks* can produce lattice dystrophy of the cornea in different families This applies to group B in wh ch the eye disease is different

(6) The same metabolic disorder which when it occurs in the ciliary nerves causes the lattice dystrophy of the cornea and when it occurs in the optic naves may cause their atrophy *is encountered judging by the symptoms* also in the *other nerves of the orbit*

Many symptoms suggest that the same metabolic disorder can even occur in the *extraorbital* nerves

Addition An autopsy was performed in one case of group B in July 1969 PAD De posits of para amyloid were found in the walls of the small and middle sized vessels of many inner organs (kidneys adrenals heart liver) The eyes were not examined.

Meeting 257 May 10–11 1968

Prof Gosta Karpe (Stockholm) *Clinical electroretinography its development and future*

Docent Birgitta Zetterstrom (Stockholm) *Electrophysiologic experience of the rods and cor es system in the newborn*

J A Castren *Electroretinographical view points of certain changes in the pig ment epithelium*

Hannu Voipio *The impo tance of electro oculography in ocular fundus diagno sis*

Ahti Tarkkanen *Retinoblastoma in Finland*

Salme Vannas & Christina Raitta *Fluorescein angiography in macu lar diseases*

and Finns (Figs 4 and 5) On the other hand the values for the Fisher Lapps accorded well with those observed for Finns and inhabitants of the Åland Islands (Forsius H Eriksson A W and Fellman J Acta ophthal (Kbh) 1964 42 224-235) Intraocular pressure was very low on an average among both the Skolt Lapps and Fisher Lapps

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Meeting 255 January 20 1968

Hannu Voipio Sigurd Werner (1898-1968) In Memoriam

Harald Teir *Physiological inflammation*

Paavo Jagerroos *Hypertension and glaucoma*

Meeting 256 March 23 1968

Ahti Tarkkanen *Report of the Rehabilitation Committee appointed by the government*

Aune Raitasalo M A (Institute of Occupational Health) *The role of the psychologist in the rehabilitation of the blind and persons with poor vision*

Aulikki Laitinen social nurse *On aid for the blind and persons with poor vision*

Heikki Aurekoski *Registration of blindness*

Christina Raitta Salme Vannas Ahti Tarkkanen & Aino Nipaavo *Abortus arte provocatus – ophthalmologic indications*

Nanny Kaunisto *Dystrophia reticulata cornea (Lattice like dystrophy of the cornea)*

Alpo Lahti J Castren S Pohjola & A Mali *Proposal for a new disability table*

Arto Juusela *Disability caused by ophthalmic diseases in the light of health insurance statistics*

Osmo Kaipainen *Topical health insurance questions*

Nanny Kaunisto *Dystrophia reticulata corneae (Lattice like dystrophy of the cornea)*

Paper read at the meeting of the Finnish Ophthalmologic Society on March 23 1968 The speaker had collected and clinically followed these patients for 23 years

Meeting 259 November 30 1968

Matti Koskenoja *The joint reception facilities of physicians in Jyvaskyla from the standpoint of ophthalmologists*

Arto Palkama & Risto Uusitalo *The superior cervical ganglion the adrenal and the function of the ciliary process*

Meeting 260 January 18 1969

Sinikka Vanttinen *Hypoplasia of the optic nerve*

Ahti Tarkkanen *Need for ophthalmological specialists in Finland*

Sinikka Vanttinen *Hypoplasia of the optic nerve*

The recent literature on hypoplasia of the optic nerve was reviewed

One new case of bilateral hypoplasia of the optic nerve was described The patient was a girl aged 8½ months whose visual acuity amounted to perception of strong light The pupils showed some reaction to light Ophthalmoscopy revealed both discs to be pale and about one third the normal size The vasculature was within normal limits The macular regions were distinguished poorly from their environment Roentgenography showed that the left optic foramen was of normal size the right one a little smaller

Pediatric and neurologic examinations at the age of 1½ years disclosed nothing abnormal with the exception of the patient s poor vision The EEG was normal

There are no members with poor vision in the patient s family and the developmental disturbance can therefore hardly be attributed to heredity A possible maternal infection in early pregnancy which had escaped detection cannot be ruled out with certainty

The speaker emphasized in agreement with earlier workers the diagnostic significance of hypoplasia of the optic nerve It is a notable cause of blindness in the bilateral cases When unilateral it may be an aetiologic factor in strabismus

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Meeting 261 March 22 1969

Antti Rantanen & Veikko Tommila *Prevalence of strabismus in Finland*

Erik Nordman *Late result after pleoptic treatment*

Heikki Aurekoski *Operative technique for c ngenital cataract*

Johannes Leikola *The use of prisms in the treatment of manifest strabismus*

Anja Mustakallio *Development of rat retina*

K A Palkama *The histochemical properties of the centrifugal fibres of the optic nerve*

Meeting 208 September 6–7 1968

Seppo Pohjola & Kari Raivio *Cataracta zonularis bei idiopatischer Hypoglykamie*

Ilkka Raivio *Incidence and distribution of uveal melanoma in Finland*

Pekka Pohjanpelto *Thyroid diseases and aqueous humor dynamics*

Johannes Leikola *Position and water drinking test*

Christina Raitta & Salme Vannas *Ueber die Pathogenese des hamorrhagischen Glaukoms*

Ahti Tarkkanen *The Annual Meeting of the European Ophthalmic Pathology Society in Paris May 1968*

Erkki Suvanto & Lauri Merenmies *Metastatisches Karzinoma der Iris und des Ziliarkorpers*

Erkki Suvanto & Lauri Merenmies *Metastatisches Karzinoma der Iris und des Ziliarkorpers*

Eine kurze Uebersicht uber metastatisches Karzinom der Uvea wurde dargestellt Die Ursachen des seltenen Vorkommens besonders in den vorderen Teilen der Uvea wurden besprochen Als eine der Ursachen wurde die Anatomie des uvealen Kreislaufes angefuhrt Das seltene Vorkommen wird jedoch scheinbar aufgefasst da das Auge bei der klinischen Obduktion zu wenig beachtet wird In 48–73 % der Uveametastasen ist der Sitz des Primartumors die Brustdruse Auf die klinischen Symptome besonders uvealer Reizung und Druckanstieg wurde aufmerksam gemacht

Ein eigener Fall ein Mann von 65 Jahren fruher gesund mit den Symptomen einer vorderen Uveitis und Druckanstieg im linken Auge wurde vorgefuhrt Thoraxrontgen zeigte einen Schatten der linken Lungenspitze Ein bronchogenes Karzinoma wurde als Ursache angesehen

Die Inflammation des Auges ging im Krankenhaus etwas zuruck aber 10 Tage nach der Hospitalisation wurde an der Iriswurzel ein rotlicher als Metastate aufgefaster Tumor festgestellt Wegen Schmerzen wurde das Auge etwa 1 Monat nach der Einweisung enukleiert

Histologisch handelte es sich um undifferentierten Karzinom das sowohl Iris als auch den Ziliarkorper infiltrierte Der Patient starb 5 Wochen spater

Die Obduktion entfaltete einen faustgrossen Tumor im oberen Lobus der linken Lunge (histologisch war er von oat cell type) sowie Metastasen der Leber Bauchspeicheldruse und Nebennieren

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Johannes Leikola *The use of prisms in the treatment of manifest strabismus*

Lauri Merenmies *Pseudotumour of the orbit*

J A Castren *Retrolental fibroplasia*

Antti Rantanen & Veikko Tommila *Prevalence of strabismus in Finland*

According to studies carried out in different countries the prevalence of strabismus and amblyopia varies considerably The differences may be great even in the same age group Thus Heinonen (1947) observed squinting in only 0 9 per cent of elementary school children in Turku whereas Frandsen (1960) established it in an average of 4 5 per cent in Danish elementary school children The frequency findings reported from other countries generally range between these two figures The range for amblyopia is 1 3–3 1 per cent according to studies conducted in some countries

Our aim in this study was to throw light primarily on the prevalence of strabismus and its various forms and of amblyopia in Finland As the investigation formed part of the international research programme of the Association of Bachelors of Medicine we also paid attention to the occurrence of errors of refraction and other anomalies in the eye The research was carried out by Bachelor of Medicine research groups under the direction of Dr A Rantanen from the Eye Hospital University Central Hospital Helsinki The State Medical Board assisted in the practical execution of the study

The study covered 2100 seven year old pupils in the first grade of elementary school in 14 localities in South Finland Seven year olds were selected because Frandsen among others had observed that squinting was commonest just in this age group The follow up study of the strabismus and amblyopia patients was done two years later at the Eye Hospital University Central Hospital Helsinki

Abnormalities of the eyes were as follows

	per cent
Manifest strabismus	4 6
Anisometropia amblyopia (amblyopia in all 1 8 per cent) (V $\leq$ 0 6)	0 5
Latent strabismus of marked degree	1 9
Errors of refraction not associated with the above which require attention about	3 0
Three other defects	0 2
Total	10 2

The different forms of strabismus were distributed as follows in the follow up examination

	per cent (of squints)
Esotropia	55
monocular	39
alternating	16
Exotropia	45
monocular	11
alternating	10
intermittent	24
Hypertropia	0

The incidence of manifest strabismus in our series was roughly the same as in Frandsen s Danish material but it was considerably higher than in Heinonen s material

Kaivonen & Koskenoja (1963) established strabismus in 2 7 per cent of children aged 4–4.5 years in the administrative district of Central Finland but the incidence of strabismus at that age is smaller than at seven and thus the figures are not easily comparable. However they seem to show fairly good correlation In addition to manifest squints there are latent squints of marked degree at some stage that require treatment They were present in 1 9 per cent of the cases This figure is difficult to compare with incidences established elsewhere

The commonness of amblyopia in our material was of roughly the same order as has been reported elsewhere It was slightly higher than in the series reported by Kaivonen & Koskenopa who gave 1 3 per cent

Of the different forms of strabismus exotropia was relatively more frequent in our series than has been reported elsewhere for children of school age The occurrence of monocular esotropia as the commonest and intermittent exotropia as the second commonest form of strabismus concurs with general experience

Johannes Leikola *The use of prisms in the treatment of manifest strabismus*

Strabismus is a condition in which the eyes look in different directions or more exactly the foveas point in different directions in the space. In the early stage, the patient has double vision which is naturally disturbing Consequently there is gradual sensory adaptation of the retina and the brain so that the image is transmitted to the brain only from one eye or alternately from both eyes or in the squinting eye another point of the retina than the fovea centralis begins to mean "straight ahead The fault is thus corrected in part, but natural binocular single vision is lost at the same time

Prisms turn the direction of the ray of light If a prism of suitable strength is correctly pos tioned before the squinting eye a situation can be created in which the rays of light from a distant point enter simultaneously the fovea centralis of the retina of both eyes This creates ideal cond tions for binocular single vision to develop as the eyes are functionally straight despite the anatomical deviation The theory is that faulty sensorial adaptation phenomena, now unnecessary or even detrimental gradually disappear

The idea has been known for some time but its application has been limited by two factors (1) the prisms have been thick and heavy (2) as the angle of squint often varies markedly especially when the situation is "disturbed with a prism the prism strength has to be changed f equently in the early phase of treatment This and light p isms of plastic so called Wafer prisms are available today and they can be conveniently attached to the patient s glasses and changed at will Pigassou (1966) described a techn que for the treatment of both concomitant and incomitant squints although the process is laborious initially It is often necessary to resort to temporary o ercorrection by means of prism

Anatomical strabismus i e the mutually faulty position of the eyes is not generally correctable w th prism therapy alone. When moderately good binocular single vision has been achieved the eyes are stra ghtened operatively Once good binocular function has been ensu ed first the eyes reta n the correct position better postoperatively

The great advantage of the method over the classical orthoptic technique is that it involves all day treatment versus 1–2 hours/day In addition viewing occurs in natural con litions without the disturbing effect of machines The method does not demand much patient cooperation and thus his age and developmental level are not such important factors

The duration of treatment ranges from three months to one year The criter a of cure are the visual axes are stra ght and the patient has complete binocular single

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Johannes Leskola *The use of prisms in the treatment of manifest strabismus*

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Prisms turn the direction of the ray of light. If a prism of suitable strength is correctly positioned before the squinting eye, a situation can be created in which the rays of light from a distant point enter simultaneously the fovea centralis of the retina of both eyes. This creates ideal conditions for binocular single vision to develop as the eyes are functionally straight despite the anatomical deviation. The theory is that faulty sensorial adaptation phenomena, now unnecessary or even detrimental gradually disappear.

The idea has been known for some time, but its application has been limited by two factors (1) the prisms have been thick and heavy (2) as the angle of squint often varies markedly especially when the situation is disturbed with a prism the prism strength has to be changed frequently in the early phase of treatment. This and light prisms of plastic so called Wafer prisms are available today and they can be conveniently attached to the patient's glasses and changed at will. Pigassou (1966) described a technique for the treatment of both concomitant and incomitant squints although the process is laborious initially. It is often necessary to resort to temporary overcorrection by means of prism.

Anatomical strabismus i e the mutually faulty position of the eyes, is not generally correctable with prism therapy alone. When moderately good binocular single vision has been achieved the eyes are straightened operatively. Once good binocular function has been ensured first, the eyes retain the correct position better postoperatively.

The great advantage of the method over the classical orthoptic technique is that it involves all day treatment versus 1–2 hours/day. In addition, viewing occurs in natural conditions without the disturbing effect of machines. The method does not demand much patient cooperation and thus his age and developmental level are not such important factors.

The duration of treatment ranges from three months to one year. The criteria of cure are the visual axes are straight and the patient has complete binocular single

vision With conventional therapy this is often impossible Pigassou who obtained the best results gave a cure percentage of 94 for a material of 109 patients without going into more detail

The method broadens the range of use of prisms from palliative to curative treatments of strabismus

Lauri Merenmies *Pseudotumor of the orbit*

The term originally included all non neoplastic tumors of the orbit (Hirschfeld 1905) Later only chronic inflammatory tumors whose etiology was unknown were termed pseudotumors Margaret Coop (1961) studied the pathogenesis of the lesion and suggested that it should be termed lipogranuloma I Blodi & J Gass (1967) in their extensive study isolated several histologic types which however showed some common characteristics The clinical and histologic findings of five cases treated at Helsinki University Eye Hospital are briefly described

Case I 50 year old man Orbitotomy according to Naffziger was performed for severe exophthalmos of the right eye The orbital tissue was filled with mononuclear inflammatory cells mostly lymphocytes 15 years later probe excision was repeated and the clinical and histologic picture was the same

Case II 43 year old man The right eye had slowly dislocated downwards over a period of two years Palpable tumor in upper orbit was extirpated Histologic finding was homogenous firm connective tissue with scanty inflammatory cells In the two years since operation the condition has been satisfactory

Case III 48 year old man Mild exophthalmos and defective movement in the right eye were seen Excised tissue showed perivascular inflammatory cells in the outer rectus muscle

Case IV 49 year old man Tumor extirpated from the outer segment of upper lid and orbit showed fibrotic lacrimal gland with profuse lymphocytes The other lacrimal gland and the parotid glands appeared normal on palpation

Case V 8 year old girl Both upper lids were swollen There were dense palpable tumors around the bulbs Histologic tissue was filled by follicular perivascular and diffusely arranged inflammatory cells including mononuclear cells eosinophils and histiocytes A special finding in this case was a high rate of blood sedimentation

In none of these cases were signs of systemic disease found nor was there any history of trauma Systemic therapy with corticosteroid improved the condition markedly in all the cases

J A Castren *Retrolental fibroplasia*

The symptoms incidence and etiology of fibroplasia in the active and cicatrisation stages were reviewed A follow up study performed by the speaker on patients who had contracted fibroplasia in the 1950 s was described The results of an investigation on the toxic effects of oxygen on both man and test animals were reported Over 70 per cent oxygen was found electron microscopically to cause disruption of the cytoplasm and pyknosis in the endothelial cells of the retinal capillaries within six hours The immaturity of the retinal vasculature was also established to have an obvious role in the genesis of fibroplasia

A theory was advanced that the completion of the retinal vasculature may occur at slightly different times in different individuals according to the Gaussian curve At one end of it would be the cases of fibroplasia in which the patient s birth weight was over 2500 g and at the other end the prematures who do not develop the disease despite oxygen therapy

Although it was believed in the 1950 s that the disease had practically disappeared

a strangely high number of cases have still been found A total of 93 new cases were diagnosed in Helsinki in 1960–1968 An etiology other than oxygen therapy might be a possible explanation. Another possibility might be the fact that oxygen therapy has again been given to prematures in recent years in concentrations of 100 per cent even especially to those with the respiratory distress syndrome If it is possible to keep the arterial oxygen pressure at about 60 mm Hg which guarantees 90 per cent saturation of hemoglobin the risk of fibroplasia should be small If the arterial oxygen pressure can be taken in hospital this presents no special difficulties but most hospitals do not have the facilities Oxygen is then administered mostly on the basis of the cyanosis of the premature child and the oxygen pressure may amount even to hundreds of mm Hg Sufficiently frequent examinations by an ophthalmologist are helpful in these cases If the premature is found to have manifest retinal vasoconstriction administration of oxygen must be immediately reduced

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Meeting 262 May 30 1969

Twenty two British ophthalmologists as guests of the meeting

M J Roper Hall (Birmingham) *Management of perforating injuries of the eye*

C Cockburn (Aberdeen) *Experiences of cryosurgery in cataract operation*

L E Werner (Dublin) *Cyclodialysis*

C A L Palmer (Sheffield) *Some problems in ptosis management*

Jouko Meretoja *A new heritable syndrome lattice corneal dystrophy*

Discussion *Nanny Kaunisto*

M J Roper Hall *Conditions simulating unilateral exophthalmos*

A McKie Reid (Liverpool) *Malnutrition of the eye*

J Donald M Gass Stereoscopic Atlas of Macular Diseases C V Mosby Co St Louis 1970 232 pages 498 illustrations and stereoscopic views on 15 VIEW MASTER® reels and a VIEW MASTER® compact viewer Price $ 48 50

This is a remarkable atlas devised principally like the stereoscopic manual of the ocular fundus by Blodi Allen & Frazier and the stereoscopic atlas of slit lamp biomicroscopy by Braley Watzke Allen & Frazier

The multitude of macular diseases and disorders are presented as black and white photographs fluorescein photographs and stereoscopic colour fundus photographs An elaborate text and careful pathophysiological explanations are characteristic for this valuable atlas The contents are divided into 12 sections with e g normal macula disciform detachment of the retina wrinkling of the choroid exsudative non exsudative traumatic and neoplastic diseases

P Brændstrup

Hugonnier R & Hugonnier S Strabismes Hétérophories Paralysies Oculo Motrices Les Desequilibres Oculo moteurs en Clinique 3 ed Masson et Cie Paris 1970 860 pages 270 figures Price 130 F

The present book is the 3rd edition of the well reputed French textbook on strabismus and related problems

The authors have maintained the original classification of six main items divided in 50 chapters (1) anatomy and physiology (2) nonparalytic strabismus sensory adaptations and heteroforia (3) paralytic strabismus (4) methods of examination (5) non surgical treatment including a comprehensive description of orthoptic treatment (6) surgical treatment

A revision has been made in accordance with the immense advances made in order to bring the book up to date This revision especially concerns the treatment of amblyopia and abnormal retinal correspondence As in former editions the present one is based on the authors personal experiences from the University Eye Department in Lyon

The book is written in a rather broad style aiming at the education of orthoptists as well as ophthalmologists

In spite of this the book is pleasant and easily read and should be recommended to those interested in ocular motility problems

K Norskov

H E Kaufman (ed) Ocular Anti inflammatory Therapy Charles C Thomas Springfield 1970 272 pp

This volume is a symposium sponsored by the National Eye Institute under the aegis of its Ocular Phamacology Task Force established in 1968

Leading clinicians and scientists contribute in a series of chapters followed by discussion essentials to our knowledge in the the intricate field of therapy of ocular in

flammatory diseases Primarily elucidated are the many aspects of stereoid medication, including the problems of steroid induced ocular hypertension Of non steroid therapy is considered the effect of antimetabolites antilymphocyte serum and immunosuppressive therapy

P Brandstrup

Cru Coke Ricardo Color Blindness an Evolutionary Approach Charles C Thomas Springfield Ill USA 156 pp 40 figures 24 tables Price $ 8 75

This small monograph has been written by a specialist in internal diseases who approaches the subject from the Chair in Medical Genetics at the University of Chile

The problems of colour vision primarily belong to ophthalmology and physiology because of their relationship to retinal biochemistry The genetic aspects of colour blindness are therefore often eclipsed by a principal interest in vocational possibilities of colour blinds or the predictive value of colour vision investigations in the diagnosis of eye diseases. On the other hand geneticists often lack sufficient basic training as concerns differentiation among the clinical types of colour blindness

The author gives a comprehensive introduction to the physics of light colorimetry and the biochemistry and physiology of visual pigments Another chapter discusses abnormalities in colour vision with special reference to colour confusions in cases of *protanopia and deuteranopia The various tests designed to detect colour blindness are* commented upon and one chapter gives an intensive survey of modern concepts of genetics

The inspiration to write this book has undoubtedly arisen from a primary interest in evolutionary biology and diseases as agents in shaping the genetic structure of the human population The discussion of the frequency of colour blindness among different races and the plotting of *isophenics* i e. zones of equal frequency of colour blindness on a map of the world is of great interest although the uniformity of a world wide screening can be questioned

In the last chapter the author gives an account of his theories concerning the connection between colour blindness and common diseases not previously combined with X linked inheritance A significant association between colour blindness and cirrhosis of the liver was found but the argument in support of alcoholism as a disease condition controlled mainly by a gene located on the X chromosome is rather complicated The presence of an acquired colour blindness in these cirrhotic patients would be more easily *comprehensible*

The book provides however so much information that it can be recommended as an introduction to the multilateral problem of colour vision.

V Dreyer

European Contact Lens Society of Ophthalmologists

First Scientific Congress Royal College of Surgeons of England London 2nd 3rd and 4th June 1971 Meeting to include kerato prosthetics Delegates should apply at once to The Congress Secretary Moorfields Hospital High Holborn London W C.1 England The registration fee includes luncheons reception and Congress banquet at the Royal College of Surgeons The fee will be Members of European and American Contact Lens Society £ 12 ($ 30) non members £ 20 ($ 50) (Non medical personnel may apply if sponsored by an ophthalmologist) Ophthalmologists in training £ 10 ($ 25)

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Department of Ophthalmology and the Blood Bank and Blood Grouping Laboratory, Århus kommunehospital, University of Århus, 8000 Århus C, Denmark

CORNEAL TRANSPLANTATION AND HISTOCOMPATIBILITY

BY

NIELS EHLERS and STEEN AHRONS

In recent years great efforts have been made to suppress the immunological reactions which may occur after corneal transplantation (for references see *Vannas* 1967, *Boke* 1968). Treatment with steroids, antimetabolites and anti-lymphocyte serum has been investigated. Whole body irradiation has also been suggested. Only recently has the possibility of reducing the immune reaction by selecting histocompatible donors and recipients been considered (*Ahrons & Ehlers* 1970, *Ehlers & Ahrons* 1971), the explanation of course being that histocompatibility testing has only been possible during the last few years.

It is the purpose of this report to present the concept of histocompatibility to an extent which seems relevant to the ophthalmologist and to report our experience regarding the importance of histocompatibility for the fate of corneal grafts in the rabbit as well as in man.

Histocompatibility

The degree of compatibility between tissues is determined by their antigenic properties. Histocompatibility or transplantation antigens may be defined as antigens on cells and tissues which after grafting induce an immune response in the recipient, resulting in rejection phenomena. This immune response is a function of the genetic disparity between donor and recipient and permits grouping of the antigens into certain histocompatibility systems.

Information on histocompatibility antigens and barriers has been obtained from animal studies, particularly studies on mice (*Snell & Stimpfling* 1966, *Snell* 1968). In

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this animal as least 11 different histocompatibility systems seem to exist (H 1 to H 11) in addition to histocompatibility factors associated with the X and the Y chromosome If a graft is transplanted from one animal to another which differ with respect to antigens belonging to these histocompatibility systems rejection will occur after a period of varying length The H 2 antigens are strong transplantation antigens and incompatibility with respect to H 2 antigens results in prompt rejection for skin grafts usually within 8–12 days Skin grafts between mice only differing with respect to non H 2 antigens show a larger survival time whereas multiple non H 2 differences reduce the survival time of the grafts (*Klein* 1967) The H 2 system is considered the *major* histocompatibility system in mice the other H systems are called *minor* systems

Recent reports by *Shreffler et al* (1970) *Snell et al* (1970) and *Thorsby* (1970) describe attempts at simplifying the H 2 system into a system similar to that found in man

Technique of histocompatibility testing Whereas determination of the blood groups for clinical purposes is now a matter of routine the identification of tissue antigens still presents problems Most commonly histocompatibility antigens are determined on leucocytes or on platelets from peripheral blood Tissue antigens are probably found on all cells of the organism

Originally an agglutination reaction was employed However this technique is rarely used now because of its poor reproducibility The introduction of complement binding techniques and in particular the lymphocytotoxic technique represents considerable technical improvements

In the lymphocytotoxic technique isolated living lymphocytes are incubated with antiserum in the presence of complement If antigens corresponding to the serum antibodies are present on the surface of the lymphocyte the latter is killed (= cytotoxicity) Dead lymphocytes are then visualized by the addition of a supravital dye e g trypan blue which stains dead but not living cells *Terasaki* & *McClelland* (1964) introduced a micro modification of this technique Modifications of their technique e g the one described by *Kissmeyer Nielsen* & *Kjerbye* (1967) are now used for tissue typing and permit the identification of the majority of antigens

A complement fixation technique using isolated platelets as antigens makes possible the identification of an increasing number of exactly the same histocompatibility antigens as determined by the lymphocytotoxic technique

Genetics of histocompatibility systems Transplantation antigenic systems have been found in all animal species They are all rather complex but appear to be determined by closely linked dominant genes in a narrow chromosomal region The inheritance follows simple Mendelian laws Antigens determined by a locus at which two or more alleles can be found and which are antigenic in individuals of the same species which lack these alleles are termed *iso antigens* or *allo antigens*

Human histocompatibility systems At present only two iso antigenic systems are known to constitute *major* transplantation antigens in man the ABO blood group system and the HL A system

The ABO system Almost all human tissues contain A and B antigens The importance of ABO antigens for the survival time of skin grafts has been demonstrated both in pre immunized and non pre immunized individuals (*Dausset* & *Rapaport* 1966 *Ceppellini et al* 1969) It has been concluded (*Kissmeyer Niel*

sen & Thorsby 1970) that the antigens A_1 and B are important human histocompatibility antigens However it is difficult to establish the original strength of the ABO compatibility barrier because pre immunization of normal individuals e g by contact with bacterial antigens may have occurred

The HL A (Human Leucocyte locus A) system According to current concepts this major histocompatibility system consists of two closely linked chromosomal loci (or subloci) on one autosomal chromosome A substantial number of different genetic determinants belong to each of these two loci and behave as multiple mutually exclusive genes This implies that *only one* gene from each of the two series can be present on each locus on each of the two chromosomes The two series of genes belonging to the two loci are called the LA (or first) and FOUR (or second) series respectively This genetic concept implies that any individual can have at most four different HL A genes (and corresponding antigens) i e two LA and two FOUR genes The extreme complexity of the HL A system is caused by the large number of genes belonging to each series The true number of genes is still unknown but today the products of at least 10 LA and 23 FOUR genes can be identified and they can be combined into about 15 000 different phenotypes (= tissue types) in unrelated individuals As the most frequent phenotype occurs in about one per cent of Caucasians it is evident that it is difficult to find histocompatible doners among unrelated persons Due to Mendelian inheritance however at least 25 per cent of siblings are HL A identical and it is therefore much easier to find histocompatible persons in families

HL A antigens are probably constituents of most normal human tissues (Kissmeyer Nielsen & Thorsby 1970) Again skin grafting experiments clearly show the importance of the HL A system in graft survival However even in ABO and HL A identical siblings first set skin grafts seldom survive for more than 20–30 days showing that antigenic systems other than ABO and HL A are of importance in graft survival In kidney transplantations a significant correlation betwen HL A and ABO matching and the clinical results has been demonstrated (Kissmeyer Nielsen & Thorsby 1970) Results of transplantation of other organs (heart lung liver bone marrow) also appear to show the importance of the HL A system

The degree of compatibility between donor and recipient is indicated by means of the letters A to G An A match means HL A identity between donor and recipient The B match signifies that the recipient has one or more HL A antigens not present in the donor but the donor does not possess antigen(s) not present in the recipient C D and E matches denote that the donor has one two or three HL A antigens not present in the recipient An F match means that the recipient has circulating antibodies agains donor antigens The G match signifies that all the possible four HL A antigens of the donor are different from those of the recipient.

Animal experiments showing the importance of histocompatibility in corneal transplantations

In an experimental study of interlamellar corneal transplantations in rabbits indirect evidence in support of the influence of histocompatibility systems on the fate of corneal grafts has recently been revealed (*Ehlers & Ahrons* 1971) As suming that strong histocompatibility antigens in the rabbit are determined by a number of closely linked genetic determinants which constitute the so called RL A system analogous to the HL A system in man the animals could be grouped as histocompatible or non histocompatible by means of 18 different lymptocytotoxic rabbit iso antisera Siblings showing the same reaction patterns to these antisera were assumed to be RL A identical or histocompatible Two series of experiments were performed

Non-pre-immunized recipients Fig 1 is a diagrammatic illustration of the results obtained by interlamellar grafting to non pre immunized recipients A slightly greater tendency to opacification is noted between the incompatible transplantations but after 3 weeks no opacification was seen either in animals with compatible or in animals with incompatible grafts Histologically a lymphocyte infiltration was seen at the corneal limbus diffusely in the stroma and around the graft As seen from Fig 1 there is a slightly greater tendency to lymphocyte infiltration in non compatible transplantations but in all cases

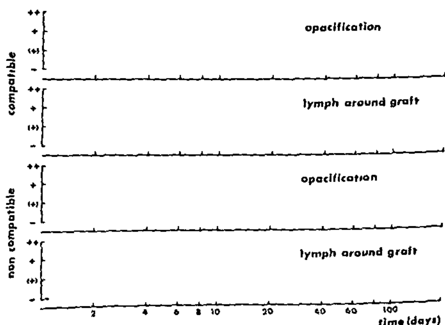


Fig 1

Diagrammatic illustration of graft opacification and histologically observed lymphocyte infiltration around graft in interlamellar rabbit allo transplantations Each point represents one animal

this cellular reaction had disappeared after 3 weeks (Fig 2) Infiltration with polymorphonuclear leucocytes occurred in many animals notably those with clinical signs of infection No correlation was found between this infiltration and the degree of serological compatibility Postoperatively conjunctival scrapings were studied for cytological changes but no convincing differences were observed between the compatible and the non compatible cases

Pre immunized recipients To detect and augment possible incompatibilities 20 animals were pre immunized by 3 skin grafts from the prospective cornea donor They were then screened for lymphocytotoxic antibodies against the donor s lymphocytes and in two cases subjected to non compatible transplantations such antibodies could be demonstrated Clinically a distinct difference between compatible and non compatible interlamellar corneal transplantations could be observed (Fig 3) Graft opacification and vascularization were seen only once in nine animals when donor and recipient were compatible but in four out of six and two out of five respectively when they were incompatible These differences are found to be probably significant by Fischer s exact test ($P < 0.04$) Histologically a significant difference ($P < 0.01$) in lymphocyte infiltration around the graft was obs rved between compatible and non compatible transplantations However all immune reactions were slight (Fig 4)



Fig 9

Interlamellar rabbit corneal allo transplantation between non compatible animals 103 days after transplantation. a Rec p ent cornea b Graft with normal epi helium No cellular infiltration s present Haematoxylin eosin

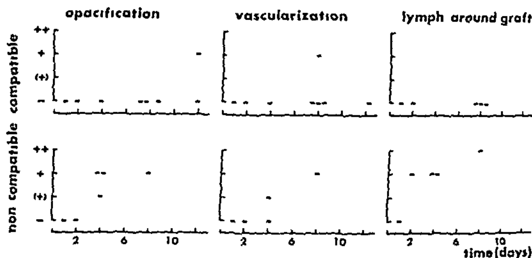


Fig 3

Diagrammatic illustration of graft opacification vascularization and histologically observed lymphocyte infiltration around graft in interlamellar rabbit allo transplantations The recipients were pre immunized by 3 skin grafts from the prospective cornea donor Each point represents one animal



Fig 4

Interlamellar rabbit corneal allo transplantation between pre immunized non compatible animals 8 days after transplantation a Recipient cornea b Graft Lymphocyte infiltration graded as ++ immune reaction Haematoxylin eosin

In the conjunctival scrapings a larger amount of lymphocytes was found after non compatible than after compatible transplantations (Fig 5)

This animal study *demonstrated that non compatible transplantations* gave rise to immune reactions whereas histocompatible transplantations did not re



Fig 5
Conjunctival smears from pre immunized rabbits subjected to interlamellar corneal allo transplantations 10 days previously a Compatible transplantation b Incompatible transplantation

sult in immune reactions not even in cases in which the recipient was sensitized by donor skin grafts It is concluded that by evaluation of donor recipient histocompatibility it will be possible to avoid immune reactions

Corneal transplantations in man

The technique of human corneal transplantations has been improved and re fined during the last decade and at present a success rate of 90 per cent or more is obtained in clinically favourable cases e g keratoconus This is in marked contrast to the transplantation of other organs in which except between iden tical twin and to some extent between HL A identical siblings it has been im possible to obtain function of a graft for more than a few days without immuno suppression In clinically unfavourable cases e g vascularized or causticated corneae good results are obtained in only about one third of the cases (*Offret et al* 1967 *Alberth* 1968) a figure which is very similar to that seen in ran domly selected kidney transplantations (*Terasaki et al* 1966)

Experimental studies have clearly demonstrated the immunological nature of many graft failures (*Maumenee* 1951 *Faure* 1964) the so called graft disease or maladie du greffon *The high rate of transparent grafts in avascular cor* neae of normal thickness may be explained by the difficult access of antibodies and cells to the tissue reducing the intensity of the antigen antibody reaction (*Faure* 1964) Apart from the normal avascularity of the cornea there are no theoretical reasons why corneal grafts should behave qualitatively differently from other grafted organs

The influence of the ABO blood group system on the results of corneal trans plantations has been studied by several authors A and B antigens were demon

strated in human corneae by *Nelken et al* (1956 1957) *Vemet* (1955) and *Sabnis & Basu* (1963) *Klen* (1955) and *Nelken et al* (1957) reported that a rise in the iso agglutinin titre occurred after ABO incompatible transplantations In contrast to these experimental studies the reports on the importance of ABO compatibility for the clinical results of corneal transplantations are rather controversial (*Havener et al* 1958 *Mehra et al* 1959 *Votockova & Karel* 1963 *Richter* 1965) In a study comprising 82 cases *Meyer* (1966) found no correlation to ABO blood group compatibility whereas *Hberth* (1965) observed a statistically significant correlation in more than 100 cases These controversial results are not surprising when it is realized that the ABO system is only one of several transplantation systems among which the HL A system seems to be the most important For obvious reasons in none of the above mentioned studies was the HL A compatibility considered However additional factors may have to be considered in explaining the conflicting results *Offret et al* (1967 1968) for example, demonstrated how the incidence of graft disease (immune reaction) increases with the diameter of the transplant i e with decreasing distance between transplanted tissue and limbal vessels

HL A antigens in the human cornea If HL A antigens influence the result of corneal transplantation they must be present in the cornea In order to investigate this seven human corneae from HL A typed corneal donors were studied

Technique Each cornea was cut into small pieces and placed in 1 ml of a balanced salt solution frozen in liquid nitrogen and while frozen homogenized with a milling cutter The homogenate was thawn at room temperature spun at 12 000 G for 4 minutes and the supernatants discarded The pellet was divided into two equal parts and one of these was incubated with monospecific HL A antiserum directed against one of the HL A antigens supposed to be present in the cornea the second was incubated with antiserum not directed against any of the possible HL A antigens of the cornea After careful mixing and incubation at 37°C for 90 minutes the tubes were spun at 12 000 G for 4 minutes The absorbed antisera were removed and a twofold titration was made in inactivated AB serum A comparison was carried out between the results obtained with absorbed and unabsorbed antisera when tested against the same positively reacting lymphocytes by the micro method of *Kissmeyer Nielsen & Kjerbye* (1967)

The results of these experiments are shown in Table I It appears that a reduction in strength (score) was only observed for the sera directed against antigens supposed to be found in the cornea not for the other sera tested This indicates the presence of the specific HL A antigens in the corneal tissue

Preliminary clinical experience The influence of histocompatibility on the results of human corneal transplantations has been studied since 1968 In view of the complexity of the HL A system and the additional necessity of considering the ABO compatibility and clinical state of the recipient cornea a large material must be supposed to be required in order to obtain a statistically significant correlation between the HL A compatibility and the clinical results Table

Table I

Absorption of monospecific HL A antisera with cornea homogenates from HL A typed donors

HL A type of cornea donor	antiserum	score		antiserum	score	
		unabsorbed	after absorption		unabsorbed	after absorption
3 9 K	anti HL A3 45569 69	12	8	anti HL A2 1626 67	10	10
3 7	anti HL A7 18017/67	7	8	anti HL A2 1626 67	10	9
2 Li FJHISI Mal	anti HL A 16 6 67	10	7	anti HL A9 45563 69	12	11
1 2 7 8	anti HL A2 1626 67	10	6	anti HL A9 45563 69	12	11
2 3 7 BB	anti HL A2 T 783 67	21	13	anti HL A12 12714/69	5	4
2 Li 12 LND	anti HL A2 8499 68	5	3	anti HL A7 18017/67	7	[illegible]
5 BB	† anti HL A2 T 783 67	8	4	anti HL A7 18017/67	7	[illegible]

Homogenates from 7 corneae were incubated with antisera directed against one of the supposed antigens of each cornea The strength of the cytotoxicity test between the sera and positively reacting lymphocytes was evaluated before and after absorption and the result given as a score

In the lymphocytotoxic test 100-76 per cent killed cells are graded as ++++ 75-51 per cent as +++ 50-21 per cent as ++ 20-10 per cent as + and less than 10 per cent dead cells as – The score is obtained by adding the + s from the reactions in a dilution series

† In this experiments the antiserum was diluted 1 8 before absorption with the cornea homogenate

II shows the results until now The cases are divided into degrees of HL A compatibility (match grades C to G) The ABO types of donor and recipient are also shown The results are graded as clear fair and opaque Among the C and D matches the results are good whereas among G matches only avascular corneae have been treated with success A case suggesting the importance of the HL A antigens for the result of the transplantation is reported below

Case report

A 47 year old man (H H) with herpetic keratitis of the left eye since May 1966 Topical treatment was given without any lasting effect and tarsorraphy was performed in August 1966 The infection recurred twice on opening the tarsorraphy the last time in 1968

On admission in January 1970 the right eye was found to be normal Examination of the left eye showed an infracentral corneal macula affecting the entire corneal thickness In the lower nasal quadrant deep vessels reached the macula There were no signs of active intra ocular inflammation A single synecchia was found otherwise the iris and lens were normal The visual acuity was reduced to hand movements the intra ocular tension was normal

On January 27 a penetrating 7 mm homotransplantation was performed The graft was fixed with interrupted sutures The post operative treatment consisted of topical atropine steroid and antibiotics Systemic 30 mg prednisone was given from the fifth post operative day The clinical course was uneventful At discharge the visual acuity was 0 33 the graft was clear without vessels and there were no signs of inflammation A check up examination on May 6 showed visual acuity 0 67 + 1 0 sph and a clear graft

On May 14 pain redness photophobia and impaired vision suddenly occurred Examination on May 17 revealed oedema of the graft with a diffuse stromal haze epithelial bullae and folds in the posterior surface There were precipitates on the posterior aspect of the graft but not on the recipient cornea There were no vessels in the graft The visual acuity was limited to counting fingers On treatment with systemic steroids topical atropine steroid and antibiotics the graft cleared somewhat but was still oedemateous Retransplantation is intended

Laboratory investigations The patient is blood group A the donor O and consequently no major ABO incompatibility was present The patient is typed HL A Ba*† 3 7 and the donor HL A 9 10 5 BB† There was thus maximum incompatibility between donor and recipient as all four donor antigens were different from those of the recipient The transplantation was graded as a G match Conjunctival smears made in the immediate postoperative period showed a normal picture with mainly polymorphonuclear leucocytes On May 6 3 months after the transplantation a change to relative lymphocytosis was observed This lymphocytosis remained after the graft rejection on May 14 and faded gradually within the next few months

Epicrisis A 7 mm penetrating transplantation was performed in a case of herpetic keratitis with deep vessels There was ABO compatibility but maximum HL A incompatibility The primary clinical result was excellent but later typical graft rejection occurred This rejection was preceded by a shift in the conjunctival cell morphology from mainly polymorphonuclear leucocytes to lymphocytes

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†Ba* = W28 BB = W10 Kissmeyer Nielsen & Thorsby (1970)

Table II

Clinical result of penetrating corneal transplantations

Case	Age	Diagnosis	HL A match grade	ABO		Observation months	Result		
				donor	recipient		clear	fair	opaque
KS	21	keratoconus	C	0	0	99	+		
MB	23	keratoconus		A	0	16		+	
KJ	24	caustic injury		A	0	18		+	
PB	33	metaherpetic	D	A	A	6	+		
IP	34	Groenouw II		0	A	20	+		
CI	35	keratoconus		0	AB	2	+		
LM	51	zoster		A	0	6	+		
DK	53	metaherpetic		A	A	6	+		
HA	[illegible]	scrofulosis		0	A	6	+		
EM	62	scrofulosis		AB	B	23	+		
FJ	62	metaherpetic		AB	B	6			+
TI	28	metaherpetic	E	0	A	2	+		
HE	30	keratoconus		0	A	12	+		
JW	51	luetic		A	0	3	+		
CK	58	metaherpetic		0	0	8			+
FM	63	scrofulosis		AB	B	3	+		
AW	66	luetic		A	0	15	+		
AJ	67	Fuchs dystrophy		0	0	9			+
HK	28	keratoconus	C	0	0	3	+		
JB	30	metaherpetic		0	0	5	+		
LF	44	caustic injury		A	AB	14			+
HH	47	metaherpetic		0	AB	12			+
PS	68	Fuchs dystrophy	F	A	A	6			+

All cases received topical ultracortenol® and from 5th postoperative day systemic prednisone 30 mg. This medication was gradually reduced in the following months. The results were evaluated by slit lamp microscopy.

Conjunctival lymphocytosis as indicator for graft rejection The conjunctival cell morphology has been followed after penetrating transplantations Conjunctival smears were taken with a blunt spatula as recommended by *Zucker & Basu* (1968) In Fig 6 the results of 10 cases are shown in diagrammatic form It appears that an increasing relative lymphocytosis occurs with a decreasing degree of histocompatibility Furthermore, it appears that in the cases with clinical rejection phenomena (indicated by arrows) these were preceded by a relative lymphocytosis However, in some cases an increased lymphocytosis was observed without clinical signs of rejections

The cell morphology seen in human conjunctivae after corneal transplantation was similar to the one observed in our rabbit experiments (Fig 5)

From the results reported in Fig 6 as well as from the reported rabbit experiments it is concluded that an immune reaction after transplantation may be observed by a study of the conjunctival cells An increased number of lymphocytes indicates an immune reaction In the cases reported lymphocytosis appeared before the actual rejection In spite of this observation no therapeutic measures have as yet been taken but in the future it would be tempting to increase steroid medication in order to suppress the rejection Antimetabolites might also be indicated in this situation

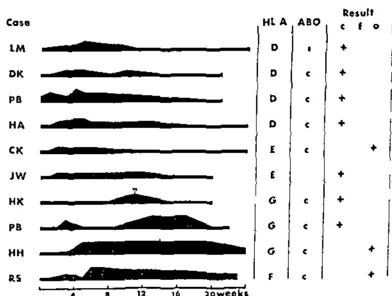


Fig 6

Diagrammatic illustration of the conjunctival lymphocytosis following human penetrating corneal transplantations Abscissa weeks after operation Ordinate lymphocytosis arbitrarily graded as – (+) + and ++ Arrows indicate clinical rejection
The columns to the right show HL A match grade ABO blood group compatibility (c compatible i incompatible) and the results evaluated by slit lamp microscopy they are graded as clear fair and opaque All cases are found in Table II

Discussion

Histocompatibility testing has profoundly changed the possibilities of organ transplantation In human kidney transplantations the HL A system has proved its value (*Kissmeyer Nielsen et al* 1970) and *Lund & Ahrons* (1970) demonstrated the importance of a similar system in rabbits *Ehlers & Ahrons* (1971) showed that this rabbit system (called RL A) influences the fate of inter lamellar corneal allografts The technique of interlamellar grafting is of course not a direct parallel to the lamellar or penetrating techniques used in human transplantations However the main result of the rabbit experiments the lack of immune reaction in compatible transplantations even after pre immunization most probably also applies to human transplantations Although the cornea owing to its avascularity constitutes a preferential site of grafting it seems highly probable that better results can be obtained by taking into consideration the degree of histocompatibility between donor and recipient It must be borne in mind that a fairly large proportion of patients will previously have had blood transfusions pregnancies and/or corneal transplantations which may have sen sitized them to histocompatibility antigens It is at present unknown whether the antigenic properties of the cornea vary with the disease

The presently available methods for preservation of the cornea (*Rycroft* 1965 *Fjordbotten* 1965 *Martinez & Paton* 1969) only allow lamellar transplantations to be performed Therefore as regards penetrating transplantations a corneal exchange programme similar to those already established for kidney trans plantations would probably be a step forward

Summary

At present only two iso antigenic systems are known to constitute major trans plantation antigenic systems in man viz the ABO and the HL A system The presence of ABO antigens in the cornea has been known for a long time In the study presented here HL A antigens were demonstrated In rabbit experiments it was shown that immune reactions may be avoided by grafting between com patible donors and recipients The same probably applies to human transplan tations Preliminary clinical results are presented and the significance of HL A incompatibility is illustrated by a case It was found that changes in the con junctival cytology reflect the corneal immune reactions in rabbits as well as in man It is suggested that conjunctival cell morphology be used as a guide for immunosuppressive therapy A cornea exchange programme as already estab lished for kidney transplantations is proposed

Conjunctival lymphocytosis as indicator for graft rejection. The conjunctival cell morphology has been followed after penetrating transplantations. Conjunctival smears were taken with a blunt spatula as recommended by *Zucker & Basu* (1968). In Fig. 6 the results of 10 cases are shown in diagrammatic form. It appears that an increasing relative lymphocytosis occurs with a decreasing degree of histocompatibility. Furthermore, it appears that in the cases with clinical rejection phenomena (indicated by arrows) these were preceded by a relative lymphocytosis. However, in some cases an increased lymphocytosis was observed without clinical signs of rejections.

The cell morphology seen in human conjunctivae after corneal transplantation was similar to the one observed in our rabbit experiments (Fig. 5).

From the results reported in Fig. 6, as well as from the reported rabbit experiments, it is concluded that an immune reaction after transplantation may be observed by a study of the conjunctival cells. An increased number of lymphocytes indicates an immune reaction. In the cases reported lymphocytosis appeared before the actual rejection. In spite of this observation, no therapeutic measures have as yet been taken, but in the future it would be tempting to increase steroid medication in order to suppress the rejection. Antimetabolites might also be indicated in this situation.

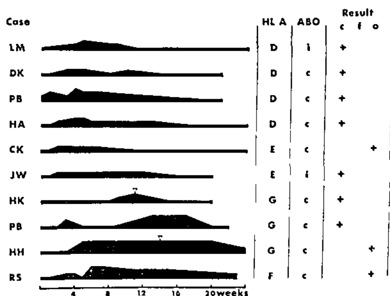


Fig. 6

Diagrammatic illustration of the conjunctival lymphocytosis following human penetrating corneal transplantations. Abscissa: weeks after operation. Ordinate: lymphocytosis arbitrarily graded as – (+) + and ++. Arrows indicate clinical rejection. The columns to the right show HL-A match grade, ABO blood group compatibility (c compatible, i incompatible) and the results evaluated by slit lamp microscopy; they are graded as clear, fair and opaque. All cases are found in Table II.

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Acknowledgement

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contain enzymes capable of reducing the substance to the coloured compound Dead cells remain unstained

The conjunctival mucus is produced by goblet cells which are found scattered all over the conjunctiva The mucus accumulates to form a long mucous thread extending through the entire inferior fornix Blinking causes it to move medially on to the skin at the inner canthus where it dries up to become sleepy seeds A similar mucous thread is present in the superior fornix (*Norn* 1969 A)

In most cases staining with iodonitrotetrazolium will show a few scattered dots in the otherwise limpid mucous thread In a few cases most of the mucous thread becomes diffusely red

The object of the present study has been to clarify why the degree of staining and thus the reducing capacity of the mucous thread may vary The mucous thread in the inferior fornix has been examined in the slit lamp and in the microscope

Slit lamp Examination

Vital staining was performed by instilling 0 01 ml of an aqueous 1 % solution of iodonitrotetrazolium into the conjunctival sac towards the temporal portion of the superior bulbar conjunctiva Blinking caused the substance to spread in the conjunctival sac The degree of vital staining was read after minimally four minutes by which time the enzyme activity had ceased

The lower lid was everted and the red staining of the mucous thread was recorded

A total of 336 eyes were examined The diagnoses and the results are shown in Table I

The staining of the mucous thread was graded arbitrarily in grades 1–5 Grade 3 represents moderate staining grade 4 considerable grade 5 maximum grade 2 minor and grade 1 absolutely minimum staining In only four cases did the mucous thread show no red colour whatever

The staining grade averaged 1 5 in normal eyes against 2 7 in acute and 2 9 in chronic infectious conjunctivitis Pronounced staining was also noticed in relation to keratoconjunctivitis sicca (2 4) to corrosion and sometimes also to vernal conjunctivitis

In normals the staining grade is independent of age and sex

Contact lens wearers and patients with corneal disorders iritis exophthalmos and chronic simple conjunctivitis showed conditions approximately like those in normals

In normal eyes only a few red dots were found scattered in the otherwise limpid mucous thread These red dots were seen to be localized medially most

Department of Ophthalmology Kommunehospitalet Copenhagen Denmark
(Heads P Brændstrup & M S Norn)

ENZYME ACTIVITY IN THE CONJUNCTIVAL MUCOUS THREAD

Iodonitrotetrazolium-Vital-Staining of the Mucous Thread in the Inferior Conjunctival Fornix

M S NORN

Everyone has a mucous thread in the inferior fornix Round and oval vacuole like formations are present in this mucous thread A compound that is capable of staining such vacuoles making it possible to determinate the contents of the vacuoles has recently been found A vital staining is indicated by means of which a distinction can be made between an infected and a sterile conjunctiva

Iodonitrotetrazolium is a colourless compound which by reduction is converted into red formazan The author of the present paper has shown in a previous paper (*Norn* 1971) that the compound is suitable for vital staining of the cornea and conjunctiva Pathological processes are stained red after a latency of four minutes

Iodonitrotetrazolium differs in principle from all other dyes employed for vital staining of the cornea and conjunctiva Unlike rose bengal for instance it rarely stains normal structures In chronic simple conjunctivitis it produces punctate staining of the tarsal conjunctiva, a phenomenon not seen after any of the other dyes employed so far

Iodonitrotetrazolium stains cells that are so degenerate that the substance can penetrate through the cell membrane but these cells are alive enough to

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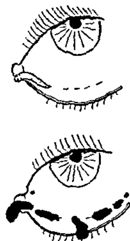


Fig 1
Diagrammatic representation of the iodonitrotetrazolium vital stained mucous thread in the inferior conjunctival fornix. Above a normal conjunctiva below infectious conjunctivitis

times apathogenic Further inoculation may give a negative result in some phases of bacterial infection

Thirdly the quantitative cytologic analysis of the conjunctival fluid, a method that gives more reliable elucidation than the bacteriological

To these may be added as a fourth possibility a distinction based on vital staining with iodonitrotetrazolium

Below the iodonitrotetrazolium vital staining will be compared with the method of quantitative cytologic analysis of the conjunctival fluid previously developed by the author (Vorn 1960)

The principle of this method is as follows

The volume of conjunctival fluid found within an area of π mm² is aspirated into a pipette of fixed dimensions The aspiration is undertaken laterally in the inferior conjunctival fornix

Presence of more than 100 neutrophilic leucocytes is characterized as neutrophilia and this is a sign of infectious bacterial conjunctivitis In normal eyes the conjunctival fluid will always contain less than 100 neutrophilic leucocytes and less than 100 lymphocytes

In one hundred cases iodonitrotetrazolium vital staining and mucous thread examination were followed by quantitative cytologic analysis of the conjunctival fluid The results are shown in Table II

In 75 per cent accordance was seen between cytology and vital staining neutrophilia being associated with a diffusely red stained mucous thread In

Table 1

Iodonitrotetrazolium vital stained mucous threads examined in the slit lamp The figures indicate the percentage numbers of patients with a mucous thread having the properties concerned The mean staining grade is based on an *arbitrary grading* of 1–5

	Mucous thread in the inferior conjunctival fornix					
	number of pts	mean staining grade	red dots	diffusely red	unbroken in inf fornix	broken into lumps
normal eyes	85	1 48	85	3	26	2
simple chron conj	56	1 93	73	2	20	[illegible]
ac infect. conj	22	2 65	0	86	64	55
chron infect conj	30	2 93	30	53	[illegible]	[illegible]
corneal disorders	30	1 40	67	10	20	17
contact lens wearers	9	1 64	87	0	11	0
keratoconj sicca	15	2 40	40	27	80	0
others	86	1 94	62	21	43	7

often in the part of the thread that had crept on to the skin at the inner canthus Such dots were never seen in the lateral portion of the mucous thread (Fig 1) A diffusely red mucous thread was found in no more than 3 per cent of the clinically normal eyes

Among the cases of acute infectious conjunctivitis on the other hand a diffusely red stained mucous thread was found in 86 per cent but never red dots alone The red colour included the whole thread often in the entire length of the inferior fornix The mucous thread may be discontinuous i e be present as lumps in the fornix (Fig 1)

Similar conditions were seen in chronic infectious conjunctivitis In non infectious disorders on the other hand the conditions were the same as in normals

Quantitative, Cytologic Analysis

It may be difficult to distinguish between a bacterially infected conjunctiva and a sterile one We have the following possibilities of doing so

First the general clinical impression based on the past history (in the first place sticking together of the eyelids in the morning) and examination in the slit lamp (hyperaemia pus)

Secondly the bacteriological analysis which cannot always give a definite answer because many bacterial species may at times be pathogenic and at other

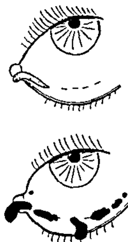


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Table II

Iodonitrotetrazolium stained mucous threads examined in the slit lamp compared with the results of quantitative cytologic analyses of conjunctival fluid 100 eyes Others comprise lymphocytosis and eosinophilia

cytology	Type of mucous thread			
	infectious	normal	mixed	Total
neutrophilia	29	10	4	43
normal eyes	4	46	2	52
others	1	1	3	5

cytologically normal eyes scattered red dots were seen in an otherwise non stained mucous thread

In 11 per cent the mucous thread became vital stained in such a manner that no definite conclusion could be drawn (transitional forms with dots as well as diffuse staining)

In 14 per cent disaccordance was noted between cytology and vital staining In 4 per cent vital staining might give occasion to unnecessary antibiotic thera py and in 10 per cent to underdiagnosing of infectious conjunctivitis

Microscopy

The iodonitrotetrazolium vital stained mucous thread was transported on two wooden sticks to a slide for microscopy The red stained portions were seen to be vulnerable the colour changing on dessication of the preparation fixation treatment with alcohol and xylol or by embedding in balsam chiefly owing to precipitation of the dye in large needle shaped crystals

When the preparation was kept in a moist chamber the colour remained unchanged for about 6 or 7 hours

Mucous threads from 190 eyes were examined The majority were examined immediately after the sampling and the remaining within two hours of transfer of the iodonitrotetrazolium stained thread to a moist chamber Physiological saline was dropped on the mucous thread which was covered by a cover slip immediately before the microscopy

Preparations of the normal type i e with scattered red dots seen in the mu cous thread in slit lamp magnification were found to contain scattered dif fusely red structureless circular or oval formations in the otherwise limpid

thread The latter consists of unstained mucous fibrils with a few unstained cells of different kinds

The red round or oval formations are from 50 to 100 μ in size They correspond to the structures described previously as vacuoles because they are neither stained by other vital stains nor by histologic stains (*Norn* 1968) Electron microscopy showed the vacuoles to contain an amorphous and possibly electronopaque substance

Preparations of the infectious bacterial type i e with a mucous thread presenting a diffuse intense red colour in slit lamp magnification consisted microscopically of innumerable weakly and diffusely red or yellow stained neutrophilic leucocytes occasionally with minor tracts of leucocytes with grains in the cytoplasm In most cases other cells with red grains in the cytoplasm (cylindric cubic and nuclear squamous epithelial cells) and extensive mucous fibril tracts filled with numerous fine red grains were also found Red vacuoles were only rarely seen

Transitional forms may occur between the infectious and the normal type In such cases the medial sleepy seeds portion of the mucous thread is of the infectious type with red leucocyte nests whereas the lateral portion has scattered red vacuoles

Quantitative Cytologic Analysis

Table III shows the results of quantitative cytologic analyses of conjunctival fluid compared with those of microscopy of the iodonitrotetrazolium vital stained mucous thread The investigation comprised 100 eyes

In [illegible]6 per cent of the cases accordance was found between the results achieved by the two methods Thus mucous threads characterized by diffuse red staining due to red leucocytes and red grains in the mucous fibrils coincided with neu

Table III

Iodonitrotetrazolium vital stained mucous threads subjected to microscopy compared with the results of quantitative cytologic analyses of conjunctival fluid. 100 eyes

cytology	Type of mucous thread			
	infectious	normal	mixed	Total
neutr philia	31	6	6	43
normal eyes	4	45	3	[illegible]
others	1	1	3	5

trophilia of the conjunctival fluid, whereas mucous threads with red vacuoles coincided with a normal conjunctival cytology

In 10 per cent there was disaccordance Of these 4 per cent presented a normal cytology together with a mucous thread marked by infection and 6 per cent showed neutrophilia and a normal appearing mucous thread Such mistaken diagnoses were found particularly among patients with keratoconjunctivitis sicca without infection and in mild degrees of neutrophilia

In 14 per cent it was impossible to decide on the basis of microscopy of the mucous thread whether the preparation was referable to the infectious type or to the normal (transitional cases)

Experimental Studies

Why are the vacuole like formations in the mucous thread stained diffusely red? The vacuoles seem to contain no cells It must therefore be extracellular substances accumulated in the vacuoles that are able to reduce the colourless iodonitrotetrazolium to the red formazan

When the mucous thread was transferred from the conjunctiva to a slide where it dried up and then was drenched with iodonitrotetrazolium the vacuoles remained unstained In a few cases the vacuoles were stained after the moist mucous thread had been transferred to the slide where it was immediately drenched first in physiological saline and thereafter in iodonitrotetrazolium Mucous threads from dead bodies remained practically unstained These experiments showed the reducing principle to be unstable

Since the commercial preparation lysozym (Sigma lot no 29 B – S010) is not stained by iodonitrotetrazolium the colour reaction can hardly be due to the lysozyme of the tears

Using iodonitrotetrazolium imbibed filter paper conjunctival fluid was sucked up in the same manner as in the Schirmer test The folded down paper end in contact with the conjunctiva was stained intensely red The staining grade corresponded to a reduction of about 4–8 per cent of the compound in the paper

Tears that had run over the lid margin were not stained however whereas conjunctival epithelial cells that had been in contact with the paper were stained *in vivo*

The colour reaction seen is presumably due to the paper damaging the conjunctival epithelial cells touching it Substance from these cells is then supposed to be sucked into the paper and cause the reaction The tears as such cannot reduce iodonitrotetrazolium

The red colour of the vacuoles might be conceived to be referable to bacteria Iodonitrotetrazolium stains living *Staph albus* colonies intensely red within less

than one minute The individual red stained cocci are visible in the microscope In the mucous thread vacuoles no bacteria are seen but only a diffuse red colour

In 14 experiments the mucous thread was transferred from the conjunctiva to nutrient agar (*Uricult ® Helsinki Finland*) on a slide incubated 35° for 24–48 hours dyed with iodonitrotetrazolium and subjected to microscopy

Vacuoles were stained only lightly or not at all in these preparations whereas cells obtained a stronger colour Bacterial colonies do not come from the vacuoles but from other parts of the mucous thread

Bacterial colonies in the mucous thread were stained intensely red The individual cocci were distinctly red and were often seen to flow in the colourless iodonitrotetrazolium fluid along the mucous thread No red dye came off from these

The diffuse red colour of the vacuoles was in other words not directly due to bacteria

The red vacuoles could be compared with other structures by double vital staining of the mucous *in vivo* Unfortunately some dyes e g merbromine were found to precipitate iodonitrotetrazolium and thus vitiate the process

The mucus specific alcian blue can be used together with iodonitrotetrazolium The mucous fibrils are stained green vacuoles and neutrophilic leucocytes still red This suggests that the reaction is independent of mucus

Sudan black stains fat Drops of fat are scarce in the mucous thread in contrast to the frequently occurring red vacuoles

Matter expressed from the Meibomian glands (sebum) was not stained by iodonitrotetrazolium Pus from meibomitis affected eyes consisted of innumerable leucocytes some of which presented red dots

After removal of the mucous thread from the inferior conjunctival fornix another one was produced which could be removed after 1/2 to 2 hours This second mucous thread was stained more intensely red and contained a greater number of red neutrophilic leucocytes and red columnar epithelial cells presumably because removal of the former thread had provoked conjunctival irritation

Corrosion by 1% silver nitrate in a conjunctiva having a normal mucous thread with red vacuoles caused the second mucous thread to become diffusely red with innumerable columnar epithelial cells presenting intensely red grains in the cytoplasm

Discussion

The observation was made in a previous study (Norn 1971) that iodonitrotetrazolium is suitable for vital staining of the corneal and conjunctival epithelia

Iodonitrotetrazolium penetrates into the cells where enzymes contained in the cytoplasm reduce the compound to the red formazan which stains the cells

The present investigation showed staining of the mucous thread in the inferior conjunctival fornix manifesting itself in normal eyes as red dots in the limpid mucous thread

Experimental studies gave results suggesting that this extracellular reduction of iodonitrotetrazolium is not directly caused by bacteria tears lysozyme fat or mucus

The extracellular reaction is possibly due to enzyme containing waste products exuding from damaged cells or to substances exuded from the blood stream or to mucous waste products In some instances foreign bodies may presumably also contribute to the reaction

I have previously subjected the vacuoles of the mucous thread to electron microscopy and polarisation microscopy (*Egeberg* & *Norn* 1967 *Norn* 1969 B) The vacuole was found to contain amorphous matter and possibly an electron opaque substance that is capable of polarizing The vacuole stained red by iodonitrotetrazolium can likewise polarize This suggests accumulation of crystalline foreign bodies and other waste products in the vacuole These waste products become enveloped in mucous fibrils and are transported by blinking together with the mucous thread on to the skin at the inner canthus The mucous thread thus constitutes an efficient band conveyor for removal of waste products (*Norn* 1969 A) Using iodonitrotetrazolium this scavenging system can be observed directly in the slit lamp in the form of red dots in the otherwise limpid mucous thread

In infectious conjunctivitis the invasion of bacteria will give rise to leucocyte emigration into the conjunctiva with increased cell disintegration and increased occurrence of a substance having the reducing properties of enzyme This substance floods the whole mucous thread diffusely the amount being too large to be enclosed in vacuoles as is normally the case

In the slit lamp we therefore did not see a few isolated red dots in a limpid mucous thread but a diffusely red thread Microscopy showed no vacuoles but rather innumerable red neutrophilic leucocytes sometimes epithelial cells with red grains in the cytoplasm and fine red grains in relation to the mucous fibrils Waste products and foreign bodies were seen to be scattered diffusely over the whole mucous thread instead of being accumulated in vacuoles

Conclusion

Iodonitrotetrazolium stains degenerate epithelial cells of the cornea and conjunctiva provided the amount of enzyme in the cell is sufficient to reduce the

compound to the red formazan This reaction is an aid towards disclosing pathological corneal and conjunctival areas e g simple chronic conjunctivitis (*Norn* 1971)

In the mucous thread of the inferior conjunctival fornix not only cells are stained but also extracellularly present substances In the non infected con junctiva such reducing substance are found accumulated in vacuoles visible in the slit lamp as isolated red dots in the otherwise limpid mucous thread

In cases of bacterial conjunctivitis (or corrosion) the mucous thread is stained diffusely red because the reducing substances spread over the whole thread and because the innumerable neutrophilic leucocytes likewise become stained

This vital staining can be employed diagnostically in cases where one desires to find out whether or not the conjunctiva is infected

A diffusely red mucous thread suggests bacterial infection Antibiotics are indicated whereas cataract extraction is contraindicated

Few red dots in an otherwise limpid mucous thread suggests a sterile con junctiva

The method must however be reckoned to give mistaken diagnoses in about 10 per cent of the cases and doubtfully correct diagnoses in another about 15 per cent A more reliable answer is obtainable by employing the more time con suming quantitative conjunctivocytologic analysis technique (*Norn* 1960)

Acknowledgement

Verner Faurby cand pharm. Department of Information the Dispensary *Kommune hospitalet* has developed the iodonitrotetrazolium filter paper method with colour gamut

The work was aided by a grant from *Komiteen til Forebyggelse af Blindhed*

Summary

The present investigation comprised examinations of 336 conjunctivae vital stained with iodonitrotetrazolium and microscopy of vital stained mucous threads from the inferior fornix of 190 eyes

In normal eyes and in eyes with non infected conjunctivae slit lamp exami nation disclosed scattered red dots in an otherwise limpid mucous thread whereas in cases of infectious conjunctivitis the mucous thread was found to be diffusely red stained

In the microscope the red dots were seen to be diffusely red stained oval or

Iodonitrotetrazolium penetrates into the cells where enzymes contained in the cytoplasm reduce the compound to the red formazan which stains the cells

The present investigation showed staining of the mucous thread in the inferior conjunctival fornix manifesting itself in normal eyes as red dots in the limpid mucous thread

Experimental studies gave results suggesting that this extracellular reduction of iodonitrotetrazolium is not directly caused by bacteria tears lysozyme, fat or mucus

The extracellular reaction is possibly due to enzyme containing waste products exuding from damaged cells or to substances exuded from the blood stream or to mucous waste products In some instances foreign bodies may presumably also contribute to the reaction

I have previously subjected the vacuoles of the mucous thread to electron microscopy and polarisation microscopy (*Egeberg* & *Norn* 1967 *Norn* 1969 B) The vacuole was found to contain amorphous matter and possibly an electron opaque substance that is capable of polarizing The vacuole stained red by iodonitrotetrazolium can likewise polarize This suggests accumulation of crystalline foreign bodies and other waste products in the vacuole These waste products become enveloped in mucous fibrils and are transported by blinking together with the mucous thread on to the skin at the inner canthus The mucous thread thus constitutes an efficient band conveyor for removal of waste products (*Norn* 1969 A) Using iodonitrotetrazolium this scavenging system can be observed directly in the slit lamp in the form of red dots in the otherwise limpid mucous thread

In infectious conjunctivitis the invasion of bacteria will give rise to leucocyte emigration into the conjunctiva with increased cell disintegration and increased occurrence of a substance having the reducing properties of enzyme This substance floods the whole mucous thread diffusely the amount being too large to be enclosed in vacuoles as is normally the case

In the slit lamp we therefore did not see a few isolated red dots in a limpid mucous thread but a diffusely red thread Microscopy showed no vacuoles but rather innumerable red neutrophilic leucocytes sometimes epithelial cells with red grains in the cytoplasm and fine red grains in relation to the mucous fibrils Waste products and foreign bodies were seen to be scattered diffusely over the whole mucous thread instead of being accumulated in vacuoles

Conclusion

Iodonitrotetrazolium stains degenerate epithelial cells of the cornea and conjunctiva provided the amount of enzyme in the cell is sufficient to reduce the

La Clinique de la Medecine Generale (Chef Olof Forssman) et la Clinique d Ophtalmologie (Chef Tore Kornerup) Centrallasarettet Boras Suede

EXAMEN DES VAISSEAUX RÉTINIENS EN LUMIÈRE MONOCHROMATIQUE VARIABLE DANS L ARTÉRIOLOSCLÉROSE ET L HYPERTRIGLYCÉRIDÉMIE

PAR

OLOF FORSMANN & TORE KORNERUP

Si l on utilise en ophtalmoscopie une lumiere de longueur d onde relativement courte – par exemple 570 mμ – les vaisseaux retiniens vont apparaitre sombres sur un fond plus clair les vaisseaux absorbent alors selectivement la lumiere tandis que la retine la reflechit Si l on utilise une lumiere de longueur d onde plus longue – par exemple 610 mμ – les vaisseaux seront a peine visibles pour devenir pratiquement invisibles a une longueur d onde encore plus longue la reflexion est a ce moment a peu près la meme a partir des vaisseaux et a partir du fond d oeil en general Entre ces deux longueurs d ondes existe un intervalle de transition Si durant l ophtalmoscopie d un seul vaisseau l on fait varier la longeur d onde vers des valeurs de plus en plus hautes on arrive a la valeur L (Kugelberg 1934) a laquelle le vaisseau disparait Si l on change alors la lumiere vers des valeurs plus courtes on obtient une valeur ou le vaisseau reparait c est la valeur K Ces variations successives de la longeur d onde de la lumiere peuvent s obtenir en utilisant un monochromateur ou des filtres continus La moyenne arithmetique de L et de K est la valeur LK LK a *ete etudiee dans* diverses conditions pathologiques de la retine (Kornerup 1947) et a ete trouvee *plus basse pour les* vaisseaux atteints d arteriosclerose que pour les vaisseaux sains Les variations de LK peuvent en principe dependre soit de l etat de la paroi du vaisseau soit de la composition du sang

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circular vacuoles in the unstained mucous thread This phenomenon was due to the presence of a substance having the reducing properties of enzymes

The diffuse red colour in infectious conjunctivitis was due to staining of innumerable neutrophilic leucocytes sometimes also other cells and scattered dye grains In cases of bacterial invasion the reducing substance was too abundant to be concentrated in vacuoles

By vital staining with iodonitrotetrazolium it is possible to distinguish between infective conjunctivitis and a sterile conjunctiva This method results in a mistaken diagnosis in about 10 per cent of the cases and in a doubtfully correct diagnosis in another about 15 per cent compared with the more reliable quantitative cytologic analysis of the conjunctival fluid

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EXAMEN DES VAISSEAUX RÉTINIENS EN LUMIÈRE MONOCHROMATIQUE VARIABLE DANS L ARTÉRIOLOSCLÉROSE ET L HYPERTRIGLYCÉRIDÉMIE

PAR

OLOF FORSMANN & TORE KORNERUP

Si l on utilise en ophtalmoscopie une lumiere de longueur d onde relativement courte – par exemple 5/0 mμ – les vaisseaux retiniens vont apparaitre sombres sur un fond plus clair les vaisseaux absorbent alors sélectivement la lumiere tandis que la retine la reflechit Si l on utilise une lumiere de longueur d onde plus longue – par exemple 610 mμ – les vaisseaux seront a peine visibles pour devenir pratiquement invisibles a une longueur d onde encore plus longue la reflexion est a ce moment a peu pres la meme a partir des vaisseaux et a partir du fond d oeil en general Entre ces deux longueurs d ondes existe un intervalle de transition Si durant l ophtalmoscopie d un seul vaisseau l on fait varier la longeur d onde vers des valeurs de plus en plus hautes on arrive a la valeur L (Kugelberg 193/) à laquelle le vaisseau disparait Si l on change alors la lumiere vers des valeurs plus courtes on obtient une valeur ou le vaisseau reparait c est la valeur K Ces variations successives de la longeur d onde de la lumiere peu vent s obtenir en utilisant un monochromateur ou des filtres continus La moyenne arithmetique de L et de K est la valeur LK LK a ete etudiee dans diverses conditions pathologiques de la retine (Kornerup 194/) et a ete trouvee plus basse pour les vaisseaux atteints d arteriolosclerose que pour les vaisseaux sains Les variations de LK peuvent en principe dependre soit de l etat de la paroi du vaisseau soit de la composition du sang

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Le but de ce travail est d apprecier l utilite de la détermination de LK pour etablir le diagnostic précoce d artériolosclérose des vaisseaux retiniens La possibilite d une hypertriglyceridemie concomitante a aussi ete prise en consideration Si le taux des triglycerides augmente la turbidite du sérum augmente aussi, dans les cas extremes le serum devient lactescent

Pour repondre a la question de base – peut on grace a la determination de LK affirmer l apparition de d arteriolosclerose dans un cas particulier – on doit déterminer la variation de LK a la fois dans une région determinee d un vaisseau donné ainsi qu entre differents vaisseaux Dans ce but on a examiné des sujets chez lesquels l arteriolosclerose pouvait s eliminer sans discussion a savoir des ecolieres agees de 10 ans D autre part pour determiner si des variations du taux des triglycerides sériques etaient suivies de variations de LK on a examiné d une part des sujets avec hypertriglyceridemie avant et apres traitement par le clofibrate d'autre part l action d une injection intraveineuse d une émulsion de graisses

Materiel d Étude

L étude de LK a éte effectuée chez 4 groupes de sujets

1 Ecolieres de 10 ans en bonne sante

2 Sujets non artériolosclereux, avant et après injection intraveineuse d emulsion de graisses

3 *Sujets avec lesions arteriolosclereuses a l ophtalmoscopie* avant et apres injection graisseuse

4 Sujets avec hypertriglyceridemie avant et apres traitement par regime et clofibrate

Méthodes

L appareillage pour la détermination de LK a deja ete décrit (Kornerup 1957) Après dilatation pupillaire le fond d oeil a été examiné a travers une lentille de Hruby dans un biomicroscope avec un agrandissement de 10 fois Un filtre d interférence pouvait etre introduit devant la fente de la source lumineuse grace a une vis micrométrique Chez chaque sujet on a choisi pour l examen dans chaque oeil 4 arterioles a leur sortie de la papille

La technique d administration intraveineuse de l emulsion de graisses est une modification de la méthode decrite par Svensson (1967) L injection a été administree le matin au sujet a jeun depuis 12 heures L injection intraveineuse de

300 ml d Intralipid® (emulsion de 20 % d huile de soja 1 2 % de lecithine et 2,5 % de glycerol) durait 3 heures a vitesse d injection constante La determination de LK etait faite immediatement avant et apres l injection La methode semi automatisee de determination du taux des triglycerides dans le serum basee sur le travail de Kesseler et Lederer (1965) donne des valeurs normales entre 80 et 180 mg %

Resultats

1 Les valeurs de LK dans les differentes regions vasculaires chez les ecolieres de 10 ans se presentent dans le tableau

Sujet nr	*Valeurs de LK*		Difference
	max	min	
1	601,5	594 6	6 9
	598 4	591 8	6 6
3	598 7	589 0	9 7
4	600 4	592 9	7,5
5	594 8	589 6	5 2

Comme il apparait dans le tableau la variation de LK entre differentes arteriole chez un meme sujet est relativement grande Cette variation n a pas de rapport avec quelqu erreur technique celle ci au double controle n atteignit que 0 75 mμ La difference pour LK entre les vaisseaux etait donc notablement plus élevee que la difference qui apparut lors de plusieurs examens d une meme partie d un vaisseau

2 Valeurs de LK apres injection de graisses chez des sujets jeunes en bonne sante

Chez un homme de 24 ans sans arteriolosclerose au fond d oeil les valeurs de LK diminuèrent d une façon significative apres l injection dans chacune des 8 régions vasculaires Chez un autre homme de 26 ans les valeurs de LK ont baisse d une façon significative dans 7 des 8 regions vasculaires examinees

3 Valeurs de LK apres injection graisseuse chez des sujets avec arteriolosclérose au fond d oeil

Chez une femme de 38 ans avec fond d oeil d hypertension II la baisse de LK a ete significative dans 6 des 8 parties des vaisseaux quoique moins prononcée que chez les 2 sujets precedents Une autre femme de 56 ans presentait un fond d oeil d hypertension prononce On a inclus dans l examen une region vasculaire avec des vaisseaux d apparence normale a l ophtalmoscopie Si la perfusion de lipides n apporta aucune modification de LK dans 7 des 8 regions vasculaires elle amena par contre une diminution de LK dans la 8eme precisement le vaisseau normal a l ophtalmoscopie Chez ces 2 femmes le taux serique des triglycerides apres injection augmenta jusqu a peu pres le niveau des sujets sans modifications arteriolosclereuses du fond d oeil

4 Valeurs de LK chez des sujets avec hypertriglyceridemie traitee Un des 5 sujets de ce groupe présentait un taux excessif de triglycerides avec sérum lactescent

Cet homme de 61 ans en bonne sante apparente sans antecédents cardiovasculaires familiaux presenta a l occasion d un examen de routine un serum lactescent Il presentait aussi un arc corneen senile L examen cardiovasculaire etait normal TA 160/100 Pas d albuminurie ni de glucosurie Uricemie 10 1 mg % Triglycérides 5000 mg % Cholesterol 428 mg % en juillet 1969 L electrophorese des lipides montra un type Fredrickson V Apres restriction des graisses et des hydrates de carbone ainsi que traitement par le clofibrate 1 gr 3 fois par jour les taux des triglycerides et du cholestérol avaient baisse de moitie en dec 1969 (500 mg % – 228 mg %) Une nouvelle electrophorese des lipides montra une amelioration (Fredrickson type IV) Les valeurs de LK en dec 1969 etaient plus elevees qu avant le debut du traitement

Chez 4 autres sujets il y avait au début une elevation moderee des triglycérides et l effet de la therapeutique a de meme ete moderee Deux d entr eux monterent pendant le traitement une augmentation significative des valeurs de LK par contre aucun changement de LK chez les deux autres Il est a noter que tous les cas de ce groupe presentaient des lésions d arteriolosclérose retinienne de degres variables

Discussion

Chez les sujets non arteriolosclereux (fillettes de 10 ans) on rencontrait donc une difference notable dans les valeurs de LK entre les differentes regions vasculaires (voir le tableau) Chez la femme de 56 ans avec une arteriolosclérose avancee (paragr 3) la valeur LK maxima etait 596 0 et la minima 588 5 différence 7 5 Ces valeurs ainsi que les differences max – min correspondent a celles enregistrees chez les fillettes D ou l on peut conclure que le diagnostic de l arte

riolosclerose par cette methode n est pas possible de toutes façons pas apres un seul examen sans chargement d Intralipid®

On peut obtenir un changement du taux serique des triglycerides de deux façons soit par injection intraveineuse d emulsion de graisses soit en faisant baisser par un traitement médicamenteux le taux des triglycerides dans les cas d *hypertriglyceridemie* Une baisse significative de LK a ete obtenue chez les hommes jeunes en bonne sante apres injection de graisses mais n a pas ete notee chez les malades avec lesions arteriolosclereuses du fond d oeil Inversement on obtint une augmentation de LK apres essai therapeutique dans les cas d hyper triglyceridemie Dans les cas ou la lipemie etait moins avancee ou combinee avec des lésions d arteriolosclérose il n y eut cependant qu une augmentation moderee ou pas d augmentation du tout LK depend donc a la fois de l etat des parois vasculaires et de la turbidite du sang

Resume

1 Par l examen du fond d oeil en lumiere monochromatique variable on peut determiner l etroite zone des longueurs d ondes ou se change l absorption de la lumière par un vaisseau La valeur numerique de cette zone est la valeur LK La valeur LK d un vaisseau depend a la fois de l etat de la paroi vasculaire et de la composition du sang Apres l injection intraveineuse d une emulsion grais seuse LK diminue dans les cas normaux et reste inchangee ou change tres peu dans l arteriolosclerose

2 La valeur de LK d une arteriole retinienne dans un cas donne depend en partie du taux des triglycérides dans le serum et en partie du degre des lesions artériolosclereuses de la paroi vasculaire

3 Dans les cas d arteriolosclerose avancee les lesions de la paroi vasculaire ren dent impossible la demonstration des alterations du taux des lipides dans le sang a moins que l examen ne porte sur une partie normale du vaisseau

4 Un abaissement therapeutique du taux des triglycerides dans les cas d hyper triglyceridemie montra une augmentation de LK Chez les sujets avec augmen tation moderee des lipides ou l effet thérapeutique avait eté modeste on a note dans certains cas une augmentation de LK dans d autres cas aucun changement

5 Un changement de LK *lors de deux examens differents* a condition que le taux des triglycerides reste inchange implique la survenue de changements dans les parois des vaisseaux

Cette methode n est pas valable pour poser le diagnostic d arteriolosclerose des vaisseaux retiniens a moins que l examen ne se fasse en combinaison avec une injection intraveineuse d une emulsion de graisses

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*Department of Experimental Ophthalmology, University Eye Clinic
Lund, Sweden*

INTRAOCULAR PRESSURE MEASUREMENT ON VARIOUS PARTS OF THE CORNEA

KENNERTH WILKE

Intraocular pressure measurements on patients with scarred and deformed corneas is often a difficult problem for the ophthalmologist since neither the Schiotz tonometer nor the Goldmann applanation tonometer give accurate readings on irregular surfaces. Using a MacKay Marg tonometer, Kaufmann et al. (1) measured the intraocular pressure on patients with scarred, edematous and otherwise irregular corneas and compared the readings with simultaneous pressure readings obtained by direct cannulation of the anterior chamber with a Sanborn manometer. There was an excellent correlation between these two sets of measurements in the pressure range of 4 to 60 mm Hg. Measurements made with the Schiotz tonometer showed great variability and gross inaccuracy. On the other hand, Stepanik (2) found that the pressure values indicated by the MacKay Marg tonometer were higher than those yielded by Goldmann's applanation tonometer. The difference between the values increased with the level on the intraocular pressure and with the rigidity coefficient. Draeger & Becker (3) found that the MacKay Marg readings under 20 mm Hg intraocular pressure were too high and over 20 mm Hg too low compared with the Goldmann readings, but the rigidity of the cornea did not affect the measurements. Follmann & Karpati (4) found that the MacKay Marg readings were much higher than those obtained with the Goldmann tonometer. Opinions of the MacKay Marg tonometer thus seem to be somewhat divergent.

There was therefore good reason to test whether another tonometer with readings well correlated to those of the Goldmann tonometer could be used on irregular corneas.

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The experiments presented here aimed first of all at finding out whether intraocular pressure varied in different parts of the cornea, and secondly whether measurements on the limbus could be used clinically in scarred irregular corneas

Method

With a vibration tonometer discribed by Krakau (5) the intraocular pressure was measured at various points on the front of the bulbs Both enucleated eyes with normal corneas and living human eyes with normal or abnormal corneas were used

The vibration tonometer consists of a small loudspeaker hung as a pendulum in a metal rod which is connected to a horizontal axis mounted on ball bearings The support is fixed to a slit lamp microscope The loudspeaker is fed from a frequency generator with an alternating current of 20 Hz In the center of the loudspeaker membrane is mounted a perspex rod to which a bar shaped piezoelectric ceramic crystal is appended The movements of the loudspeaker membrane are transferred via the comparatively stiff crystal to a plastic tip which rests on the corneal surface during the measurements The contact surface of the tip is spherical (1 5 mm radius) The instrument rests upon the cornea with a constant force corresponding to 0 3 gr When the tip is resting on the cornea a vibrating counterpressure is felt by the crystal Provided there is constant contact between the instrument and the corneal surface a practically sinusoidal current of the same frequency as that of the loudspeaker is produced After rectification the current is measured and recorded as an ink written curve

The measurements last for 10 15 sec and are repeated after about one minute At least two consecutive stable readings are required for a significant pressure value Blinking and other interferences from eye movements are easy to recognize (Fig 1) This tonometer has the advantage of enabling us to measure the intraocular pressure with very small contact surfaces between the tonometer and the cornea and with a very slight force acting upon the cornea Moreover the readings can easily be repeated at short intervals

Measurements on enucleated eyes

The enucleated bulbs were canulated and connected to an open manometer system The measurements were made on the central part of the cornea while the manometer pressure was increased in steps from 7 5 to 42 mm Hg The measurements were then repeated on the limbus in the same eye while the manometer pressure was changed as before

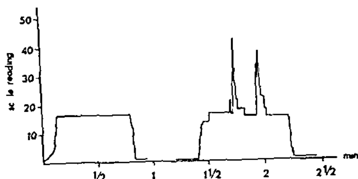


Fig 1

To the left an ideal measurement from the vibration tonometer To the right a measurement disturbed by two artefacts caused by blinkings Pulse waves etc. are effaced by a high damping of the recorder

Both rabbit eyes and human eyes were measured There was a good correlation (r = 0 998) between the manometer measurements and the vibration tonometer measurements (Fig 2)

Measurements on living human eyes

Repeated measurements from the middle of the cornea to the sclera

All patients were given 0 4 % Novesin solution in both eyes and were examined in the same room by the same doctor The vibration tonometer and the applanation tonometer were placed side by side and were used immediately after each other

On three people measurements were taken in 7 8 different places along the horizontal meridian from the central part of the cornea to the sclera A small fixation light was placed 4 cm straight in front of one eye and was then moved 1 cm horizontally in the same direction before each measurement (Fig 3) There was no change in the readings from the cornea. On the sclera however the readings were higher but they did not seem to be representative of the intraocular pressure On these patients the corneal radius was measured in the horizontal meridian with a Zeiss Keratometer in horizontal and vertical axis in four different places from the middle of the cornea to the limbus Moderate astigmatism did not change the readings (Fig 4)

Measurements on eyes with varying intraocular pressure

On 76 patients with intraocular pressure varying from 8 to 46 mm Hg meas

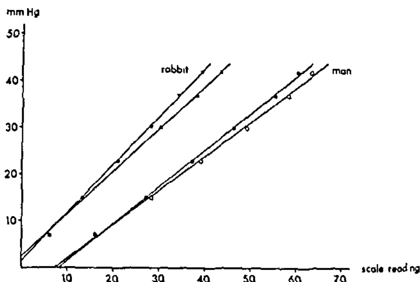


Fig 2

Measurements (scale readings) from the vibration tonometer compared to the real intra ocular pressure measured with an open manometer in an enucleated rabbit eye and in an enucleated human eye when the pressure was increased in steps from 7 to 42 mm Hg Black rings and triangles mean measurements from the middle of the cornea Open rings and triangles mean readings from the limbus

urements were made first in the middle of the cornea and 1–2 mm from the limbus with the vibration tonometer and then in the middle of the cornea with the applanation tonometer In one patient there was a difference of 4 mm Hg in another 3 mm Hg but in all the other patients the difference was not more than 2 mm Hg between the measurements taken in the middle of the cornea and those taken on the limbus with the vibration tonometer The correlation coefficient between these two different measurements was 0 994 The correlation coefficient between the measurements from the middle of the cornea taken with the vibration tonometer and those taken with the applanation tonometer was 0 96 (Fig 5)

Clinical Application

Case I A 56 year old woman with advanced keratoconus in the left cornea Before operation it was not possible to measure the intraocular pressure with either the Schiotz or the Goldmann tonometer With the vibration tonometer there were readings corresponding to 5 mm Hg on the central part of the cornea and 1[illegible] mm Hg near the normal limbus a discrepancy which is explained by the thin wall and the abnormally short radius curvature in the central part of the cornea After a penetrating keratoplasty

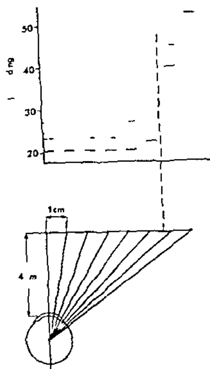


Fig 3

Intraocular pressure measurements from different places on the anterior surface of three living eyes Below is shown how the measurement direction was changed before each measurement The vertical broken line corresponds to the limbus

measurements taken on the 15th postoperative day corresponded to 8 mmHg both on the graft and on the limbus

Case II A 54 year old woman with a central keratitis in the left cornea for many years After a spontaneous perforation a penetrating kerotoplasty followed. After the operation there were synechias between the iris and the graft line and the graft was edematous Measurements taken with the vibration tonometer showed readings corre *sponding to 8 mm Hg in the middle of the graft and near the limbus which seemed* to be normal The Schiotz or the Goldmann tonometers could not be used in this post operative state After three days treatment with Diamox there were readings corre p n lin to 14 mm Hg and the patient could successfully be reoperated

Discussion

The experiments showed that both in enucleated and living eyes the scale readings obtained with the vibration tonometer were practically independent

Fp	0		15		25		35	
	0	90	0	90	0	90	0	90
I	84	81	86	83	86	82	96	84
II	93	92	93	92	93	92	98	93
III	78	74	78	74	79	74	82	75

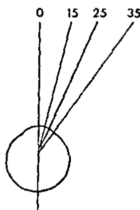


Fig 4
The corneal radius from three patients (same as in Fig 3) measured in horizontal and vertical axis along a horizontal meridian

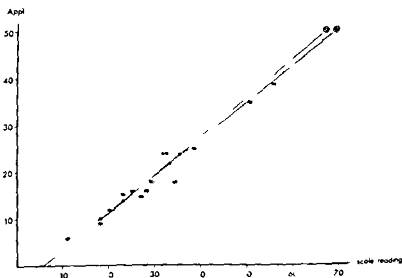


Fig 5
The vibration tonometer readings (scale readings) from .. patients compared to measurements taken with a Goldmann applanation tonometer Black rings correspond to measurements from the middle of the cornea and open rings correspond to readings near the limbus

of the place of contact between the instrument and the cornea at least along a horizontal meridian The rigidity of the corneal wall influenced the scale reading although the slope intraocular pressure versus scale reading seemed to remain unchanged as has been shown previously (5) The corneal radius too influenced the readings A smaller corneal radius gives a lower scale reading of the same intraocular pressure The measurements on rabbit eyes were in agreement with this observation since the corneal tissue of the latter is thinner and the radius slightly smaller than in human eyes (6)

Measurements on the abnormally thin and curved central areas of the cornea in cases of keratoconus can therefore not be expected to give reliable pressure estimates Fortunately peripheral parts often seem to remain unaffected by the pathological changes The experiments make it probable that the pressure readings obtained outside the changes are representative of the true intraocular pressure

Summary

With a vibration tonometer (5) the intraocular pressure was measured in different parts of the cornea using enucleated and living human eyes In living eyes there was a good correlation (r=0 96) between the measurements obtained by the vibration tonometer and those by a Goldmann tonometer Intraocular pressure measurements with a vibration tonometer near the limbus seem to be a valuable method on patients with deficiencies in the middle of the cornea but with a normal limbus

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University Eye Clinic Lund Sweden

SURGICAL TREATMENT OF CORNEAL DISORDERS

BY

ARVID ANSETH & ERIK PALM

During the last few years the treatment of corneal disorders has greatly improved the principles have been stabilized and now seem to have been generally agreed upon The technique for keratoplasty has been improved the indications widened and settled A certain tendency towards centralization has appeared which has certainly contributed to the improved results

At the University Eye Clinic in Lund rather standardized indications and surgical routine have been followed during the last decade and a comparatively uniform clinical material is now available The principal features of our experience in Lund are presented here including present indications surgical routine and results

Surgical Technique

In most ophthalmic centres in the world keratoplasty has become a standard surgical procedure During recent years the surgical technique has been developed to an exact and safe procedure greatly due to the use of microscope and refined suture material which allows an exact adaptation of the wound edges Thus the tissue reaction caused by the operation is diminished and the sutures can be kept in place for a longer period of time ensuring a firm healing with a minimal risk of wound rupture

Penetrating keratoplasty is the technique usually performed and is in most cases a safe and correct procedure At the clinic in Lund the operation is usually performed under local anesthesia A maximal miosis protects the lens during the operation The graft is secured with sutures of virgin silk During the last few years a running suture has sometimes been used but if the host

cornea is fragile or thin and rich in pathological vessels interrupted sutures 16 or more are preferred At the end of the operation the anterior chamber is filled with sterile saline and/or air to prevent contact between the wound and the iris The wound is carefully inspected for signs of leakage in which case extra sutures are placed

Lamellar keratoplasty is used in superficial pathological processes e g corneal dystrophies in early stages In active keratitis or in cases with abundant ingrowth of pathological vessels the operation is usally performed as a therapeutical or preparative operation In many of these cases a later penetrating optical keratoplasty is planned

An operating microscope makes it possible to remove practically all the stroma within the operation area down to Descemet s membrane The graft is secured with a minimum of 8 interrupted sutures of virgin silk In many cases of corneal dystrophy deep keratitis and maculae cornea the lamellar operation has been preferred to the penetrating keratoplasty especially on patients of advanced age Even with a perfect technique and the best postoperative care a penetrating operation means a somewhat greater risk for postoperative complications than a lamellar keratoplasty A successful penetrating operation usually gives a better optical result and most corneal surgeons prefer this technique On the other hand with a modern microsurgical technique the visual results of the lamellar keratoplasty are usually quite sufficient Penetrating keratoplasty is usually preferred when the pathological changes are afflicting or situated close to Descemet s membrane within the optical zone or if signs of endothelial dystrophy are observed

Postoperative Care

Penetrating keratoplasty There has been a change in the postoperative treatment of penetrating keratoplasty during the last few years Our patients are now allowed to get up with a monocular dressing on the first postoperative day A certain moderation in physical activity is required for some days This change in treatment is most of all the result of an exact and secure suturing technique As a rule the patient leaves the hospital 2 weeks after the operation and the sutures are removed after approximately 6 more weeks In vascularized corneas where isolated sutures are generally used it is often necessary to remove the sutures earlier to avoid ingrowth of vessels in the graft

1% atropin is given one to three times a day until the postoperative iritis is healed Local steroids are given in case of pronounced postoperative reactions Signs of immune reaction call for intensive local and mostly also parenteral steroid therapy for varying periods of time

University Eye Clinic Lund Sweden

SURGICAL TREATMENT OF CORNEAL DISORDERS

BY

ARVID ANSETH & ERIK PALM

During the last few years the treatment of corneal disorders has greatly improved the principles have been stabilized and now seem to have been generally agreed upon The technique for keratoplasty has been improved the indications widened and settled A certain tendency towards centralization has appeared which has certainly contributed to the improved results

At the University Eye Clinic in Lund rather standardized indications and surgical routine have been followed during the last decade and a comparatively uniform clinical material is now available The principal features of our experience in Lund are presented here including present indications surgical routine and results

Surgical Technique

In most ophthalmic centres in the world keratoplasty has become a standard surgical procedure During recent years the surgical technique has been developed to an exact and safe procedure greatly due to the use of microscope and refined suture material which allows an exact adaptation of the wound edges Thus the tissue reaction caused by the operation is diminished and the sutures can be kept in place for a longer period of time ensuring a firm healing with a minimal risk of wound rupture

Penetrating keratoplasty is the technique usually performed and is in most cases a safe and correct procedure At the clinic in Lund the operation is usually performed under local anesthesia A maximal miosis protects the lens during the operation The graft is secured with sutures of virgin silk During the last few years a running suture has sometimes been used but if the host

local and parenteral steroids in some cases for several months. If the reaction starts early after the operation the prognosis is relatively poor unless the treatment is continued for several months A prolonged steroid therapy is unfortunately not without risks and of course the patient has to be under careful general control

Lamellar keratoplasty In case of postoperative infection with swelling and necrosis of the graft the transplanted tissue has usually been replaced by fresh material Ingrowth of vessels in the operating bed is best prevented by local steroid therapy If for some reason steroids are not considered advisable good anti inflammatory effect is obtained with a 10 % Tanderil ointment Postoperative edema in the graft and the host cornea is reduced with local dehydrating therapy as soon as the epithelium covers the graft A good dehydrating effect has been obtained by Ophtasiloxane solution (Ophtasiloxane G Ferrensbach Kaysersberg Pharmacien France)

In some cases especially after chemical injuries epithelial defects in the graft remain for a long time and eventually atrophic ulcers develop in the central part of the graft In these cases a replacement of the graft with fresh donor material is necessary

Material

From 1958 to 1968 305 keratoplasties were performed on 265 eyes Most of the operations were made on optical indications in cases of a seriously altered corneal curvature (keratoconus) or greatly reduced transparency after healed keratitics chemical or mechanical injuries or degenerative disorders with corneal disposits Some cases have been operated on therapeutical indications to remove degenerated tissue in an active keratitis in order to promote the healing

In some cases the corneal process was extremely destructive and operation was the only way of saving the bulb

The material is presented in 5 diagnostic groups keratoconus viral keratitis maculae corneae corneal degenerations and dystrophies and corneal injuries

Keratoconus

The keratoconus material of the clinic has been published in two previous reports (Anseth 1966 1967) where also the general features of the disease and its treatment were discussed Table I shows the results of 87 operated eyes In

Slit lamp inspection of the wound area and the anterior chamber the first postoperative days is considered important making an early intervention possible against complications

Lamellar keratoplasty The patient gets up with monocular dressing the day after the operation without any restrictions in normal physical activity Usually local steroids are given from the same day atropin only in case of iritis

The sutures are as a rule removed 2 weeks after surgery and the patient leaves the hospital one or two days later

Operative and Postoperative Complications

Penetrating keratoplasty The operative failures have been greatly reduced with our present technique of careful and exact suturing under an operative microscope and by reforming the anterior chamber with saline or air to avoid contact between the iris and the wound area

An empty chamber on one of the first postoperative days requires a careful inspection in the slit lamp In cases of leakage the graft is immediately re sutured and the anterior chamber reformed If the wound is well adapted and if all the sutures are in place waiting for a few days while using intensive treatment with stron mydriatics often results in a spontaneous reformation of the anterior chamber without anterior synechias If this therapy fails an active reformation of the anterior chamber with detachment of the anterior synechias is performed At the same time one or more iridectomies corresponding to the wound area should be made in order to secure a connection between the posterior and anterior chamber Thus the development of glaucoma is avoided if anterior synechias should develop

Prolaps of iris in the wound is a complication that needs immediate operative intervention The sutures on each side of the protruded iris are removed and the iris is replaced in the anterior chamber This is mostly achieved by a careful injection of acethylcholin (Acetylcholinchlorid 5 mg/ml Hoffmann La Roche & Co Basel) into the anterior chamber In most cases contraction of the iris sphincter muscle pulls the protruded part of the iris back in place but in some cases a careful use of a blunt spatula is needed to restore the normal anatomy The sutures are replaced and the anterior chamber filled with air

Postoperative infections have usually been overcome with local and/or parenteral antibiotics

An immune reaction can appear any time after the first postoperative week It starts with signs of iritis and an edema of the graft The treatment has been

local and parenteral steroids in some cases for several months If the reaction starts early after the operation the prognosis is relatively poor unless the treatment is continued for several months A prolonged steroid therapy is unfortunately not without risks and of course the patient has to be under careful general control

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Table I
Keratoconus (87 eyes)

Number of eyes	Postoperative vision			Postoperative complications			Re operations
	Improved	Unchanged	Impaired	Leakage	Infection	Immune reaction	
87	84	2	1	7	2	3	1

84 of these *the visual acuity improved mostly to normal values* and in all the vision was sufficient for practical use In two eyes no improvement of vision was obtained in one because of cloudiness of the graft in connection with postoperative infection in the other a case of keratoglobus in a mentally retarded patient the graft remained clear but no increase in visual acuity was registred One eye was infected in connection with the removal of the sutures and was eventually excised because of panophtalmitis Fortunately the other eye in this patient had been operated on one year earlier *with good results*

A 7 mm trephine has been used in the majority of the operations even in advanced cases with thinning of the cornea within the operation area No un favourable effects have been observed from this routine procedure more likely the low percentage of immune reactions in the material is a result of using a relatively small size trephine in all cases Immune reaction was observed in 3 eyes in which a larger trephine was used (9 mm in two and 8 mm in one eye) Two of these grafts cleared more or *less completely after intensive steroid* therapy one graft became opaque but after retransplantation the graft re mained clear

That ultimately clear grafts were obtained in all but 2 eyes could partly be explained by the high quality of the donor material used A prerequisite for clear grafts in penetrating keratoplasty is generally agreed to be a well func tioning endothelial cell layer All grafts in the present material were used within 24 hours *of the death of the donor* and *most of this time* the donor eye was kept at +4 C

Viral keratitis

In an earlier report the results in 25 of these cases were published (Anseth & Palm 1967) The promising results from these first cases stimulated a continu ation along *the same lines*

Table II shows the results of therapeutical keratoplasty in 54 eyes suffering

Table II
Viral keratitis (54 eyes)

Type of operation and number of eyes	Improved postop vision		Unchanged or impaired postop vision			Reoperations
	Healed after first operation	Healed after reoperation or conserv treatment	Healed after first operation	Healed after reoperation or conserv treatment	Not healed	
Lamellar 36	18	6	5	7	0	15
Penetrating 18	9	3	4	0	2	

from viral keratitis in an active stage The diagnosis was *keratitis herpetica* in 52 eyes and *keratitis e vaccinia* in 2 eyes

Healing of the keratitis was obtained in 36 eyes after the first operation Reinfection was observed in the other 18 eyes In 8 of these healing was obtained after one more keratoplasty In 6 eyes healing of the reinfection was obtained without operation In 4 eyes more than one reoperation was performed two of these healed but two eyes were ultimately removed because of panophtalmitis

Improvement of the visual acuity was obtained in 36 eyes in spite of the fact that all operations were performed for therapeutical and not for optical reasons

In most of the cases the lamellar technique was used even when a preoperative descemetocele was present It seems important that all infected tissue and also all the ingrowing vessels be removed This often means the total removal of the corneal stroma down to the level of Descemet s membrane within the operation area

In some eyes the postoperative reaction was very strong with a reactive dilatation of the pathological vessels in the host cornea edema in the whole corneal tissue and an imminent risk for invasion of vessels in the grafted area making the use of steroids and sometimes Tanderil imperative In some cases the graft has been replaced with fresh material in order to counteract the inflammatory response from the surrounding tissue.

It is obvious that the majority of keratoplasties are performed on corneas in a very bad condition As a rule a stromal edema was present before the keratoplasty due to a toxic involvement of the endothelium Therefore a slight postoperative corneal edema has usually remained for some time even in cases

with primary healing In most of these eyes the tendency for postoperative edema has been controlled by a small dose of local steroids

Maculae corneae

This group consists of healed cases of different corneal diseases The results of keratoplasty in 60 eyes are presented in Table III

Keratitis phlychtenulosa represents the largest group with 32 operated eyes The results in these cases are good Increase in vision was obtained in 27 eyes in 4 eyes the vision remained unchanged and in one eye it decreased postoperatively The reasons for unsatisfactory results were in 2 eyes edema of the graft

Table III
Maculae corneae (60 eyes)

Diagnosis	Number of eyes	Type and number of operations		Postoperative vision		
		Lamellar	Penetrating	Improved	Unchanged	Impaired
Keratitis phlychtenulosa	32	17	15	27	4	1
Bacterial keratitis	6	4	2	6	0	0
Pterygium	6	8	0	6	0	0
Leucoma adherens	6	4	2	2	3	1
Sclerokeratitis	3	1	2	1	2	0
Trachoma	2	2	0	2	0	0
Dermatitis herpetiformis	2	2	0	1	1	0
Keratoconjunctivitis sicca (sec)	1	1	0	1	0	0
Buphtalmus	1	0	1	0	1	0
Phtisis bulbi	1	1	0	1	0	0

after cataract extraction and in one eye, rupture of the wound resulting in anterior synechias and cloudiness of the graft In 2 eyes no obvious reason was found

Penetrating technique was used in 15 and lamellar in 17 eyes The reason for the high percentage of lamellar keratoplasty is the relatively high age af the patients in this group

Bacterial keratitis This group includes 6 eyes with central opacities after healed keratitis of bacterial origin Improvement of the vision was obtained in all cases

Pterygium Six eyes with pterygium involving the optical zone were operated wtih improvement of vision in all cases A combination of central and partial peripheral lamellar keratoplasty was performed in 4 of the 6 eyes In two of these a reoperation within the central area was performed because of the development of non transparent material in the interspace between the lamellar graft and the host cornea

Leucoma adherens These are spontaneously healed cases after rupture of the cornea due to infectious or penetrating injuries The chances for successful operations in these badly damaged eyes are minimal as the risk for postoperative edema and immune reactions is imminent

Penetrating keratoplasty was performed in 2 eyes and lamellar in 4 A slight increase in vision was obtained in two eyes one lamellar and one penetrating the latter an autotransplantation of the corneal periphery including part of the sclera In three eyes (2 lamellar and one penetrating) the vision remained unchanged and in one eye (lamellar) the vision decreased postoperatively

Sclerokeratitis This group includes 3 eyes in two patients The eyes were in a bad condition with scleral and corneal thinning In one eye a slight increase in vision was obtained by a lamellar keratoplasty Penetrating keratoplasty was performed in 2 eyes both grafts remained opaque due to immune reaction and no increase in vision was obtained

Trachoma In 2 eyes with relatively superficial corneal opacities increase in visual acuity was obtained with lamellar keratoplasty

Dermatitis herpetiformis In two eyes with corneal opacities in connection with this skin desease lamellar keratoplasty was performed with a slight increase of vision in one eye In the other eye the graft remained clear but no increase in vision was registered

Keratoconjunctivitis sicca secundaria In this eye a removal of the lacrimal gland had been performed years before because of epiphora Superficial corneal opacities eventually developed and the local symptoms from the eye were identical with those of the sicca syndrome After lamellar keratoplasty the vision improved slightly and the local symptoms were less accentuated The observation time is 3 years

Buphtalmus Penetrating keratoplasty was performed in an advanced case

of buphtalmus with leucomatous cornea The graft remained edematous and no increase in vision was obtained

Phtisis bulbi A report on this case has been published (Anseth & Halldén 1968)

Dystrophia et degeneratio cornea

The results of keratoplasty in 39 eyes in 9 diagnostic groups are presented in Table IV

Lattice degeneration This group includes 17 eyes in 11 patients In 9 eyes penetrating keratoplasty was performed and in 8 eyes lamellar Improvement of vision was obtained in 15 eyes One eye was reoperated because of anterior

Table IV

Dystrophia et degeneratio corneae (39 eyes)

Diagnosis	Number of eyes	Type and number of operations		Postoperative vision		
		Lamellar	Penetrating	Improved	Unchanged	Impaired
Lattice degeneration	17	8	10	15	1	1
Dystrophia cornea	7	1	7	5	2	0
Endothelial dystrophy	2	0	2	2	0	0
Bandshaped degeneration	1	0	1	1	0	0
Xerophtalmia	3	6	0	2	1	0
Keratitis neuroparalytica	3	3	0	2	1	0
Keratitis bullosa postop	3	2	1	0	3	0
Ulcus rodens	2	2	0	1	1	0
Cornea plana	1	0	1	0	0	1

synechias and clouding of the graft due to postoperative leakage The second graft did not clear and a decrease of vision was noted

In 4 of the penetrating operations leakage was observed during the first post operative days A possible explanation for this inadequate tightness of the wound is lack of normal swelling properties in the wound area of the host cornea. Pathological changes in the polysaccharide pattern in corneas suffering from lattice degeneration have been demonstrated (Anseth 1969) Because of this obvious risk for postoperative complications regarding penetrating kerato plasty in lattice degeneration the lamellar technique is preferred at present.

Corneal dystrophy A more adequate diagnosis was not found in this group The corneas at the first examination were all edematous and evenly opaque 7 eyes in 4 patients were operated penetrating in 6 and lamellar in one eye In 3 of the eyes operated with penetrating technique the graft re mained opaque One of these was reoperated with good result Increase of vision was ultimately obtained in 5 eyes

Endothelial dystrophy (Fuchs) Penetrating keratoplasty was performed in 2 eyes with advanced Fuchs dystrophy The grafts have remained clear for 3 and 1 year respectively

Band shaped degeneration Penetrating keratoplasty performed elsewhere had resulted in a cloudy graft After retransplantation and cataract extraction the graft has remained clear and the vision normal for nearly 7 years

Xerophtalmia Both corneas in one patient showed thinning of the stroma and a multitude of ghost vessels Lamellar keratoplasty improved vision in both One eye in another patient with active inflammation and central ulcer ation of the cornea was operated with lamellar keratoplasty three times In tensive postoperative reaction and recurrence of the ulcer appeared each time

Neuroparalytic keratitis Lamellar keratoplasty was performed in 3 eyes because of corneal ulcer Delayed healing with edema and peripheral necrosis of the graft was observed in all cases In spite of this a slight increase in vision was registered in two cases In one eye a small peripheral tarsoraphia was performed postoperatively

Bullous keratopathy (postop) In two eyes the condition was due to failure in penetrating keratoplasty and in one eye the bullous keratopathy followed a cataract extraction In two of the eyes some relief of the symptoms was ob tained after keratoplasty In one eye the cornea was ultimately covered with a conjunctional flap because of recurrence of the symptoms

Rodent ulcer Partial lamellar keratoplasty was performed in 2 eyes No recurrence of the disease has been observed for 3 and 2 years respectively In one eye increase in vision was registered

Cornea plana An attempt to perform a penetrating graft failed because of rupture of the wound in the extremely thin tissue and the eye was eventually removed

Corneal Injuries

This group includes 25 eyes in 8 groups according to the cause of the injury The results of keratoplasty are shown in Table V

Lye Seven eyes in 6 patients were badly damaged by solutions containing lye They all healed with loss of corneal tissue scarring of the remaining cornea ingrowth of vessels and symblepharon In 5 eyes lamellar keratoplasty was performed once In only one of these was a slight improvement of vision obtained In one eye 3 lamellar keratoplasties were performed with necrosis of the graft each time Because of an imminent risk of perforation a subtotal penetrating keratoplasty was done The graft is now slightly edematous and the vision has improved One eye perforated because of the injury and healed with anterior synechias During the healing glaucoma developed In this eye a 180° rotation of the central cornea cataract extraction and removal of anterior synechias were performed A fistulating operation normalized the intraocular pressure Unfortunately the cornea remained edematous and the vision decreased

Lime Only 2 eyes were operated because of lime burns The healed stages after these injuries are similar to those injured with lye

In one eye a lamellar keratoplasty was performed once with no improvement *In one eye 7 operations were performed 4 lamellar* and 3 penetrating The first 6 grafts eventually became opaque and smelted away The last penetrating graft healed with relatively mild reaction from the surrounding tissue but remained edematous and partly opaque No increase in vision was obtained

Glue (acetone) One eye badly injured by glue was operated 4 times No

Table V
Corneal injuries (25 eyes)

Diagnosis	Number of eyes	Type and number of operations		Postoperative vision		
		Lamellar	Penetrating	Improved	Unchanged	Impaired
Lye NaOH	7	8	2	2	4	1
Lime	2	5	3	0	2	0
Glue (acetone)	1	3	1	0	1	0
Acid	3	7	0	0	3	0
Ammonia	1	0	1	1	0	0
Hot solutions	2	1	1	2	0	0
Electrical burn	1	0	1	1	0	0
Foreign bodies	8	8	1	8	0	0

improvement in vision was obtained but the eye is quiet with minimal local symptoms.

Acid One eye injured with phosphoric acid was operated once with lamellar technique The graft became opaque and no increase in vision was obtained Both eyes in a patient were exposed to acid from a car battery for approximately one hour The anterior part of the eyes including the cornea was badly injured Three lamellar keratoplasties in each eye have been performed with unsatisfactory result due to delayed healing and slow decomposition of the graft.

Ammonia Clear graft and improvement of vision was obtained in one eye

Hot solutions Exposure to boiling water gave a totally opaque cornea Increase in vision was obtained by lamellar keratoplasty

Boiling apple sauce resulted in necrosis of the central cornea and descemetocele Penetrating keratoplasty healed the keratitis and improved the vision

Electrical burn Improvement of the vision was obtained with penetrating keratoplasty

Foreign bodies In 3 eyes the corneas contained foreign bodies after explosion injuries Lamellar keratoplasty increased vision in all the eyes in one after reoperation

In 5 eyes central corneal scars due to foreign bodies were removed by lamellar keratoplasty in 4 and penetrating in one eye Increase in vision was obtained in all eyes

Conclusions and Summary

Results are presented from the last eleven years of corneal surgery at the University Eye Clinic in Lund Sweden 305 operations were performed on 265 eyes Surgical technique postoperative care, complications and special problems within each diagnostic group are discussed

Our lines of treatment and results mainly coincide with those from other ophthalmic centres Following the experience from our clinic we would stress the following points

Keratoconus In most cases an initial attempt is made with corneal contact lenses. In advanced cases with extreme protrusion thinning and scarring of the cornea keratoplasty is usually performed primarily All cases with contact lenses are checked 1-2 times a year and keratoplasty is performed if symptoms of serious discomfort or signs of progress of the disease appear

Successful results depend on the services of a trained operating and nursing staff and the cooperation of a skilled and experienced contact lens technician

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Successful results depend on the services of a trained operating and nursing staff and the cooperation of a skilled and experienced contact lens technician.

Under these conditions the results are excellent in a high percentage of the cases

Viral keratitis The lack of effective antiviral chemotherapeuticum makes keratoplasty an important treatment of deep viral keratitis Operation in an earlier stage of the disease before serious damage to the endothelium is produced will certainly increase the number of successful cases

Maculae corneae and dystrophia et degeneratio corneae Keratoplasty is the only treatment available in these cases Further development in surgical technique and postoperative treatment are prerequisites for still better results

Corneal injuries Chemical burns are still the big problem among the injuries of the anterior segment of the eye In "healed cases the results of keratoplasty are not encouraging

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10 % Tanderil ointment was supplied by Geigy Basel

University of Oslo Department of Ophthalmology
Rikshospitalet Oslo

THE PUPILLARY DILATATION CURVE AFTER MYDRIATICS

BY

MARTIN DAVANGER

In a recently published paper (Borthne & Davanger 1971) the effect of two different mydriatics cyclopentolate 1 % and phenylephrine 10 % was studied in two different age groups one group consisting of young individuals 19–25 years old and another group consisting of old individuals 60–75 years of age In the work mentioned the course of the curves given by plotting the diameter of the pupil versus time was determined for the two different mydriatics and in the two age groups In the present work the ascending part of these curves will be further analysed

The *material* and *methods* are described in the previous paper The diameter of the pupil was measured every 5 min during the first ½ hour and thereafter every 10 min during the following hour in 15 young and 15 old subjects who were given cyclopentolate in one eye and phenylephrine in the other eye The curves which will be analysed are given by the average values of these measurements

Inspection of the curves suggested that the plotted points might approximate modified exponential curves This was tested by curve fitting The 6 last values of the ascending parts of the experimental curves (each 5 min from the 5th to the 30th min after cyclopentolate and each 10 min from the 20th to the 70th min after phenylephrine) were used in the curve fitting procedure The parameters of an equation

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$$p = p_\infty - (p_\infty - p) e^{-\alpha(t\ t)} \qquad (1)$$

giving best approximation to the 6 measured values were determined In this equation p is the diameter of the pupil p_∞ is an asymptote, the value towards which p approaches when $t \rightarrow \infty$ (the last of the measured values lies close up to p_∞) t is the time in minutes after the application of the drug t is the time of the first measured value used in the curve fitting procedure p is the value of p at t = t α is a constant determining the slope of the curve at a given point.

The values found for p_∞ p t and α for cyclopentolate and phenylephrine, in the young and in the old group, are given in Table I

In Figs 1 and 2 the curves given by eq (1) are drawn and the measured values are plotted The curves approximate well the experimental data after a lag period which lasts 5 min for cyclopentolate and for phenylephrine 15 min for the old and 25 min for the young individuals

It is noted that the approximate exponential part of the curves starts when the pupil has reached a size of about 4 5 mm in all groups namely 4 78 and 4 67 mm in the young and 4 32 and 4 33 mm in the old group for cyclopentolate and phenylephrine respectively This is respectively 0 67 0 61 0 82 and 0 83 mm above the resting size of the pupil while the range of the exponential part of the curves is in the same order 3 22 2 34 2 10 and 3 48 mm

The time constant $T = 1/\alpha$ of the exponential phase of the pupillary dilatation is for cyclopentolate 5 32 and 4 63 min (young and old group) and for phenylephrine 15 3 and 12 5 min. The ratio T_{young}/T_{old} is similar for both drugs namely about 1 2

From eq (1) it follows that

$$\ln(p_\infty - p) = \ln(p_\infty - p) - \alpha(t - t) \qquad (2)$$

where $\ln(p_\infty - p)$ is a constant This means that by plotting $p_\infty - p$ versus t on semilogarithmic paper a straight line will be the result This is demonstrated

Table I

		p_∞	p	t	α	T = 1 α
Phenylephrine 10 %	Young	7 98 mm	4 64 mm	5 min	0 188 min^{-1}	5 32 min
	Old	6 68 mm	4 25 mm	5 min	0 216 min^{-1}	4 63 min
Cyclopentolate 1 %	Young	6 91 mm	3 58 mm	20 min	0 0654 min^{-1}	15 3 min
	Old	7 85 mm	5 50 mm	20 min	0 0 99 min^{-1}	12 5 min

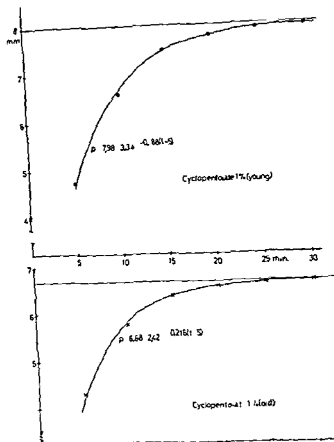


Fig 1
The approximation of the pupillary dilatation curve after Cyclopentolate to a modified exponential curve The measured values are indicated by ○ and ×

in Fig 3 The straight lines representing eq (2) approximate well the measured values which are plotted in

Differentiation of equation (1) yields

$$\frac{dp}{dt} = \alpha(p_\infty - p) \tag{3}$$

This means that after mydriatics the pupil tends to dilate with a speed which is proportional to the difference between the maximal pupillary size ($\sim p_\infty$) and the actual size At each point this speed is determined by the value of α

$$p = p_\infty - (p_\infty - p\ )\, e^{-a(t\ t\ )} \qquad (1)$$

giving best approximation to the 6 measured values were determined In this equation, p is the diameter of the pupil, p_∞ is an asymptote the value towards which p approaches when $t \to \infty$ (the last of the measured values lies close up to p_∞) t is the time in minutes after the application of the drug t is the time of the first measured value used in the curve fitting procedure p is the value of p at t = t a is a constant determining the slope of the curve at a given point

The values found for p_∞, p, t and a for cyclopentolate and phenylephrine in the young and in the old group are given in Table I

In Figs 1 and 2 the curves given by eq (1) are drawn, and the measured values are plotted The curves approximate well the experimental data after a lag period which lasts 5 min for cyclopentolate and for phenylephrine 15 min for the old and 25 min for the young individuals

It is noted that the approximate exponential part of the curves starts when the pupil has reached a size of about 4 5 mm in all groups namely 4 73 and 4 67 mm in the young and 4 32 and 4 33 mm in the old group for cyclopentolate and phenylephrine respectively This is respectively 0 67 0 61 0 82 and 0 83 mm above the resting size of the pupil while the range of the exponential part of the curves is, in the same order 3 22 2 34, 2 10 and 3 48 mm

The time constant $T = 1/a$ of the exponential phase of the pupillary dilatation is for cyclopentolate 5 32 and 4 63 min (young and old group) and for phenylephrine 15 3 and 12 5 min The ratio T_{young}/T_{old} is similar for both drugs, namely about 1 2

From eq (1) it follows that

$$\ln(p_\infty - p) = \ln(p_\infty - p\ ) - a(t - t\ ) \qquad (2)$$

where $\ln(p_\infty - p\ )$ is a constant This means that by plotting $p_\infty - p$ versus t on semilogarithmic paper a straight line will be the result This is demonstrated

Table I

		p_∞	p	t	a	$T = 1/a$
Phenylephrine 10 %	Young	[illegible] 98 mm	4 64 mm	5 min	0 188 min^{-1}	5 3[illegible] min
	Old	6 68 mm	4 25 mm	5 min	0 216 min^{-1}	4 63 min
Cyclopentolate 1 %	Young	6 91 mm	3 58 mm	20 min	0 065[illegible] min^{-1}	15 3 min
	Old	7 85 mm	5 [illegible]0 mm	20 min	0 0[illegible]99 min^{-1}	12 5 min

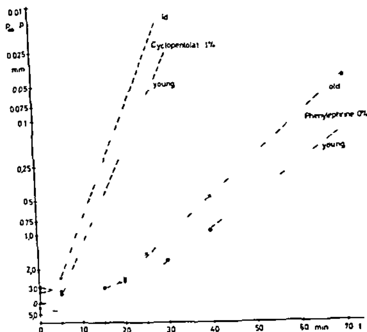


Fig 3

Pupillary dilatation curves (modified) after mydriatics indicated by ○ and × plotted on semilogarithmic paper The approximation to straight lines is demonstrated.

the quantity of the mydriatic in iris increases for a longer period as demonstrated by the prolonged dilatation of the pupil The cornea probably represents a reservoir from which diffusion into the eye takes place long after the mydriatic *has disappeared from the tear film*

The rate of transfer from the cornea to the aqueous is governed by Fick's law which applied to the present case says that the concentration of the mydriatic in the aqueous at each point changes at a rate which is proportional to the difference between the concentration in the cornea (C_c) and in the aqueous (C) That is

$$\frac{dC}{dt} = k(C - C) \tag{4}$$

where t is the time and k is a proportionality constant

By the application of this law and by taking into account the loss of the agent both from the cornea and from the anterior chamber Jones & Maurice (1966) have arrived at an equation

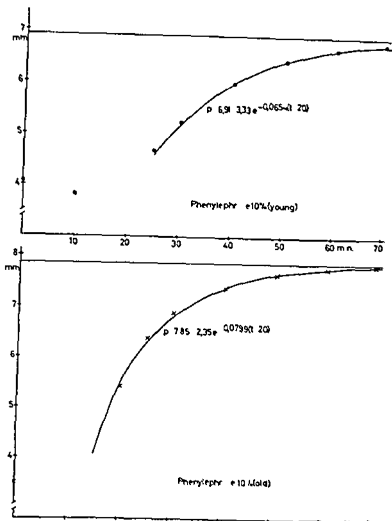


Fig 2

The approximation of the pupillary dilatation curve after Phenylephrine to a modified exponential curve The measured values are indicated by ○ and ×

It may be of interest to discuss the reason for the exponential course of the pupillary dilatation curve after mydriatics

The effect of mydriatics is so slow as compared with the speed of the pupillary dilatation e g after reduction of the illumination that an influence of viscoelasticity in the iris tissue may not be taken into account The speed at which the pupil dilates at a certain point of the dilatation curve far from the maximal size is probably mainly determined by the rate of change of the quantity of the mydriatic in the iris tissue at this point This rate of change is again determined by the rate of transfer from the eye surface to iris

Because of the turn over of the tear fluid the agent has practically disappeared from the tear film at an early stage of the pupillary dilatation curve Yet

Summary

It is demonstrated that the pupillary size versus time curve after the application of a mydriatic follows a modified exponential curve after a lag period which lasts 5 min after Cyclopentolate 1 % and 15–25 min after Phenylephrine 10 %. The exponential phase of the curve starts when the pupil has reached a size of about 4.5 mm. In the exponential phase the pupil dilates with a speed which is approximately *proportional to the difference between the maximal and the* actual size of the pupil. The reason for the exponential course of the curve is probably that the concentration of the mydriatic in the iris tissue increases after a modified exponential equation.

Acknowledgments

I thank Dr A. Borthne for his permission to use data from our joint work published recently.

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$$C_a = C(e^{-At} - e^{-Bt}) \qquad (5)$$

which is thought to apply for the concentration in the anterior chamber as a function of time. In this equation A and B are constants given by the transfer coefficients between the cornea and the aqueous and the loss coefficient from the anterior chamber and the constant C is dependent on the initial concentration in the cornea.

According to their results based on experiments with fluorescein the C_a versus time curve is dominated by the B exponential during the first 1–2 hours during which the change of the A exponential is of only small importance. Without introducing substantial error the A exponential may be considered constant for the ascending phase of our curves. Then follows from eq. (5)

$$C_a = \text{Constant} - C\, e^{-Bt} \qquad (6)$$

The transfer through the anterior chamber is probably rapid because of the termal current of the aqueous. The time taken to reach equilibrium between the aqueous and the iris tissue is probably short compared with the rate of transfer from the cornea to the aqueous. Therefore we may be justified in putting $C_i = C_a$ where C_i is the concentration of the mydriatic in the iris tissue and accordingly

$$C_i = \text{Constant} - C\, e^{-Bt} \qquad (7)$$

According to this theory the concentration of the mydriatic in the iris increases as a modified exponential function of time as given by eq. (7) which is of the same type as eq. (1). This seems to be the reasonable explanation for the modified exponential course of the pupillary size versus time curve as it is indicated by eq. (1).

The curve demonstrating the dilatation of the pupil after mydriatics flattens gradually towards the maximal value and the time taken to reach the maximal size is not sharply defined. The constant a which is an indication of the slope of the curve may give additional information on the effect of a mydriatic in addition to the statement of the average maximal size of the pupil and the time taken to reach this maximum. In our curves the maximal size is reached after minimum 4.6 and maximum 6.5 times the time constant $T = 1/a$.

According to our results the value of a is not influenced by the maximal pupillary size obtained with a particular mydriatic. This size is determined mainly by the specific interaction between iris and the mydriatic and not so much by the rate of transfer from the eye surface to iris.

The lag period before the exponential phase of the pupillary dilatation has started may be explained by the time of the uptake of the mydriatic in the cornea and the passage through the corneal tissue. It is noted that the lag period increases with decreasing a in our four experimental groups and roughly approximates to one time constant.

Material and Methods

The basic material comprises all patients with congenital or early ascertained cataract admitted to the Eye Department of Copenhagen Municipal Hospital between 1921 and 1945 inclusive on the condition that they were under 20 years of age at the time of their first operation The material has been collated from *15 324 case histories from the period in question* A number of patients were primarily excluded these include traumatic cases heterochromatic cataract microphtalmus with cataract trisomy (Down s syndrome) with cataract and a single case of congenital glaucoma with cataract A total of 78 patients remained

In 19 case histories evidence was found of other cases of *congenital cataract* in close relatives whereas 59 cases could be regarded as sporadic and thus constituted the proband material Of these 59 patients 30 were men and 29 women 18 had unilateral cataract and the remaining 41 had bilateral cataract 47 had been operated before the age of 10 years but 12 had been operated between the age of 10 and 20 years

By means of the National Register it was possible to trace all probands and only in two cases was cooperation refused Eight patients were dead and had no children One further proband was dead but the offspring were contacted We have been in touch with the remaining 48 probands and have obtained information on possible offspring At the same time all probands were requestioned on possible cases of congenital cataract in their families The probands were further questioned on the visual acuity of their children and this information was supplemented by obtaining the results of school sight tests Children whose visual acuity was in doubt or who were under school age were tested In addition all children with cataract were examined

35 probands had a total of 75 children The remaining 14 living probands had no children Of the latter group 6 were married and 8 unmarried Two of these were in institutions for the mentally deficient

Representativity

The material was collected at the only municipal eye clinic in Copenhagen and includes all cases seen in the clinic over a period of 25 years During the same period a number of patients from the same geographic area were treated at the Copenhagen University Hospital (Rigshospitalet) but there is no reason for assuming that pecial conditions determined whether a child with con genital cataract was admitted to one hospital or the other The material may therefore be considered to constitute a representative sample of cases of spo radic congenital cataract It should be noted that the material does not represent 25 birth years The oldest of the probands were born in the period 1900 to 1910 and the youngest in the period from 1940 to 1945

From the Department of Ophthalmology Kommunehospitalet Copenhagen Denmark
(Heads P Brændstrup and M S Norn)
and the University Institute of Human Genetics
Tagensvej 14 Copenhagen Denmark (Head J Mohr)

GENETIC COUNSELLING IN SPORADIC CASES OF CONGENITAL CATARACT

BY

S JENSEN AND E GOLDSCHMIDT

Congenital cataract is a frequent cause of amblyopia or blindness in children Familial as well as sporadic cases are seen and they may be either unilateral or bilateral

The genetic forms can be classified in accordance with their appearance and mode of inheritance Quite often cataract appears as the only abnormality but is also encountered as a link in more widespread hereditary ophthalmic or systemic diseases The etiology of sporadic cases is only partially known and in every series there is always a large group for which the etiology is unknown It must be assumed that some of the patients represent new mutations but as neither the mutation rate nor the proportion of cases of purely environmental origin is known genetic counselling is subject to considerable uncertainty in sporadic cases As the hereditary forms of congenital cataract most frequently follow regular dominance and as it is clinically impossible to differentiate between mutations and phenocopies genetic counsellors in Denmark have hitherto tended to the view that it is impossible to exclude the possibility of a 50 per cent risk of congenital cataract in the descendents of sporadic cases

This somewhat unsatisfactory formulation provides the basis for the present investigation which seeks to evaluate the empirical risk of the offspring of cases of sporadic congenital cataract contracting the same disease

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children or because only 50 per cent of their children are expected to be affected

The investigation has thus shown that 4 out of 35 probands with offspring (1?1 per cent) have had similar cases among their children

On the basis of this material a statistical calculation gives 99 per cent confidence limits of 2 0–31 8 per cent This means that the risk of children of cases of sporadic congenital cataract being afflicted with the same disease is quite considerable

Comments

The investigation shows that only a part of the cases of sporadic congenital cataract are likely to be due to mutations The remaining cases are phenocopies In the present material it is only probands with bilateral cataract that have had children with the disease so it is possible that the risk is greater in the cases of bilateral than of unilateral cataract Most cases of sporadic unilateral cataract are undoubtedly exogenous but it is well known that unilateral cataract *can occur in families with bilateral cataract* and the same is known from many other inheritable eye diseases e. g retinoblastoma high myopia and congenital glaucoma

In the present material it has not been possible to classify the probands on the basis of the cataract s appearance since data on this point have been sparse The four probands who have children with cataract do however represent different types – dense whitish cataract zonular cataract and nuclear cataract

Empirical risk figures represent only rough average estimates and in individual counselling their possible use must be carefully weighed In congenital cataract a number of environmental factors are known and it is therefore important to carry out a careful anamnesis in a search for environmental factors that may have caused the cataract The origin and composition of the present material does not permit calculation of the rate of mutation but it may seem surprising that *four new mutations should arise in loci for congenital* cataract in a limited geographic area within comparatively few years In the municipality of Copenhagen in the period in question, there were about 10 000 births annually which gives a comparatively high estimate of the rate of mutation since the mutations found here must be considered to be an absolute *minimum* On the other hand in evaluating new mutations it is likely that there are various loci carrying genes for congenital cataract and it is always necessary to take extra marital conception into consideration The investigation thus provides no basis for assuming that the rate of mutation for genes producing cataract should be any higher than the estimates obtained for other loci

Results

The final proband material consists of 35 probands, 12 of whom have unilateral and the remainder bilateral cataract The 35 probands have a total of 75 children seven of whom have cataract (Table I) All four probands with affected children have bilateral cataract Three of these probands each have

Table I
Number of children in 35 families

Number of children	Number of families
1	10
2	18
3	2
4	3
5	1
6	1

two children with cataract and one has one child with cataract (Fig 1) It will be seen from the figure that we have been able to follow the disease for three generations in two of the families and it is probably true of all four families that the congenital cataract in the proband has been caused by a dominant mutated gene Besides the four probands who have children with congenital cataract there may well be other probands with similar mutations that have not become apparent either because the probands have had no

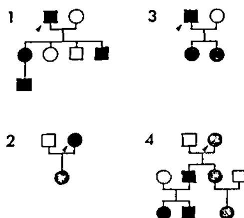


Fig 1
Families with congenital cataract

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[Dep]thalmology (Chiefs P M Moller M D and E Goldschmidt M D)
[Dep]artment of Clinical Physiology (Chief J Fabricius M D)
[Oden]se University Hospital DK 000 Odense Denmark

[OXYGEN] TENSION IN THE ANTERIOR CHAMBER OF THE RABBIT EYE

BY

J K WEGENER & P M MØLLER

The object of the present study was to arrive at a simple and reproducible method for measuring the oxygen tension in the human aqueous humour *in vivo* as a number of eye diseases may be imagined to be due to changes in the oxygen content of the aqueous humour

The oxygen tension in this medium would be expected to be intermediate between the Po in arterial blood (80–100 mm Hg) and that in mixed venous blood (40 mm Hg) However lower values were conceivable considering that e g muscles during exercise may show a Po of zero

Measurements of the oxygen tension in the aqueous humour have been done previously by various methods The results are listed in Table I

Method

Principle of measurement electrode and function of apparatus

We used the polarographic method by means of which the differences in voltage arising during the electroreduction of the oxygen are measured

Our electrode was an oxygen microelectrode from Beckman based upon the principle of Clark and primarily constructed for continuous measurements of the oxygen tension in arterial blood

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It must be concluded that cases of sporadic congenital cataract are most frequently due to environmental factors but that the risk of possible offspring getting the same disease seems to be about 10 per cent and may be higher especially in the case of bilateral cataract Further research is both desirable and necessary in this field

Summary

A total of 78 patients were treated for congenital cataract at the Eye Department of Copenhagen Municipal Hospital during the period 1921–1945 59 cases were sporadic, and an investigation has been made into the frequency of cataract in the offspring of these cases It was possible to trace 57 of the probands and 35 of these had a total of 75 children Four probands had offspring with congenital cataract, and the empirical risk for the children of patients with sporadic congenital cataract lies at between 2 0 and 31 8 per cent on the 99 per cent level The risk is presumably somewhat higher for the children of bilateral cases and somewhat lower for the children of unilateral cases Further research is both desirable and necessary in this field

thalmology (Chiefs P M Møller M D and E Goldschmidt M D)
partment of Clinical Physiology (Chief J Fabricius M D)
se University Hospital DK 5000 Odense Denmark

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Received February 18 19 1

Table 1
Oxygen tension in aqueous humour (mm Hg)

				Po mmHg Mean ± SD or SE	Range	°C	Method
de Haan	1922	rabbit	7 eyes	24.4	18–31	body tp	Krogh's microtonometric
Friedenwald & Pierce	1937	dog			40–50	37°	Nitrogen in the anterior chamber
Heald & Langham	1956	rabbit	35	48.2 SE 2.58	26–80		Polarographic
Drenckhahn & Lorenzen	1958	rabbit	13	36	21–46	37°	Polarographic
Neumann	1958	rabbit	25 eyes	52.6 ± 3.3 %		37°	Polarographic
Kleifeld & Neumann	1959	man	12 eyes	52.6 ± 5.3 %	37.5–67.5	37°	Polarographic
Jacobi	1966	rabbit	19 eyes	31.0 SD 6.12	22.9–42.8	tp ant chamber 34.3°	Polarographic

SD Standard deviation
SE Standard error of the mean

The Beckman electrode consists of a 10 μ platinum wire embedded in a glass mantle which however leaves the tip of the platinum wire free The anterior part of the electrode is covered with a cone like polyethylene membrane 25 μ thick enveloping a 3% solution of potassium chloride The membrane shields the electrode and is only permeable to gases Around the platinum cathode there is a cylindrical silver anode The electrode is further protected by a steel cylinder and is small enough to fit into a 1 1 mm needle The electrode is connected to a Radiometer pH meter type PHM 27 and Gas Monitor type I HA 927 b and the result may be read directly when diffusion equilibrium has been attained across the membrane this takes about 45 seconds

The read values are directly proportional to the oxygen tension independent of the Pco but dependent upon the temperature the diffusion rate of the oxygen increasing with increasing temperature Therefore we supplemented our investigations by measurements of the temperature in the anterior chamber of the eye

Animal Material

The experimental animals were adult albino rabbits of both sexes weighing 2 5–5 kg (mean 3 324 kg SD 0 45)

Urethan 2 5 g was administered subcutaneously and this anaesthesia was supplemented by thiopental sodium (Leopental Leo 25 mg/ml) injected into an ear vein After tracheostomy the rabbits breathed spontaneously atmospheric air conveyed at a flow of 2 l/min Through a catheter in the femoral artery the blood pressure was checked by an electrocondenser manometer and through a three way cock blood samples were withdrawn for Po Pco and pH determinations

The Po in arterial blood was also measured with a Clark electrode (Radiometer Po electrode type E 5046) The pH was recorded by an Astrup micro equipment The Pco was calculated on the basis of Siggaard Andersen s curve *monogram* Blood samples were analysed at 38° C In addition the administered quantity of thiopental sodium and urethan was recorded and the time interval from their administration to the measurement of Po in the anterior chamber

Experimental Procedure

A limbus based conjunctival flap was dissected in the upper quadrants and at the limbus most of the cornea was cut to facilitate insertion of the needle through which the microelectrode was applied the membrane being situated

in the obliquely cut tip of the needle The results were read at the end of one minute Blood samples were withdrawn immediately before and immediately after the puncture of the chamber

Immediately after removal of the needle with the electrode the temperature in the anterior chamber was measured partly with closed and partly with open eyes through the same corneal incision by a needle shaped thermopile (Electric Universal Thermometer, type TE 3 with Needle Applicator type K 19)

Calculation

The Beckman microelectrode was adjusted before and after each measurement at 37°C the zero point being fixed in an oxygen free solution (200 mg sodium sulfite in 10 ml 0 01 M sodium borate) Another point represented the oxygen tension in atmospheric air measured in distilled water through which atmospheric air was conveyed continuously

The Po_2 may then be calculated on the basis of the following equation

$$Po_2 = \frac{(B - a) \times O_2 \%}{100}$$

where B is the barometric pressure a the partial pressure of the water vapours at the temperature concerned and O_2 the oxygen content in vol % in atmospheric air (20 93 vol %)

Values were rejected if the calibration before and after the puncture of the anterior chamber differed by more than 6 per cent from the oxygen tension level in atmospheric air and by more than 3 units on the Radiometer scale in the oxygen free solution

As is apparent from Table II and Fig 1 the sensitivity of the Clark electrode to temperature is considerable but linear in the studied temperature range

Table II

Temperature sensitivity of the Beckman microelectrode measured in distilled water through which atmospheric air was constantly bubbling

C	34	35	36	37	38
mm Hg O_2 readings on the meter	122	132	143	153	16[illegible]

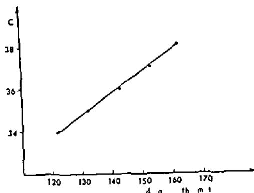


Fig 1
Temperature sensitivity of the Beckman microelectrode

Results

In a material comprising 25 eyes single measurements showed in the anterior chamber of moderately dilated pupils oxygen tensions of 10 – 60 mm Hg and a mean Po_2 value of 30 5 mm Hg SD 11 7 (37° C 760 mm Hg) There was no difference between the 17 right and 8 left eyes in the 19 rabbits 0 8 > P > 0 7

In 16 eyes the temperature in the anterior chamber was 35° 71 C SD 0 89 with open eyes and 36 39 C SD 0 87 with closed eyes The measurements were done on the same 16 eyes and on paired comparison P < 0 0001

After correction of the temperature in the anterior chamber the recorded Po value had to be corrected by a maximum of 5 per cent and the corrected Po value was 3? mm Hg

In the ?5 experiments the Po in arterial blood was ?6 9 mm Hg SD 12 4 and the Pco in the arterial blood 3? 9 mm Hg SD 4 3

The quantity of thiopental sodium was 4 84 ml SD 1 62 and the quantity of *urethan 2 5 g The time interval from their administration until the measure*ment of Po in the anterior chamber was 42 1 min SD 10 89 and 168 8 min SD 49 35 respectively

Discussion

The primary aqueous humour ought to be ideal for Po potentiometric measurements the solubility and diffusion coefficient of oxygen being as in physio

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°C	34	35°	36	37	38
mm Hg O_2 readings on the meter	122	132	143	153	162

ture but owing to admixture of secondary aqueous humour *fluid from the* posterior chamber and air we *abandoned this method*

Jacobi *used the same* Beckman microelectrode and our mean values are the same although the analytic techniques differed We read the result at the end of 1 minute Jacobi used continuous recording 10–30 minutes after puncturing the chamber and in 3 of his experiments the oozing aqueous humour was re placed by physiological saline without the Po after 20 minutes differing from the other values

Heald & Langham have stated that the choice of anaesthesia is not an im material factor In 35 rabbits anaesthetized with Nembutal the mean oxygen tension was 48 2 mm Hg SE 2 58 and in 20 conscious rabbits it was 55 2 mm Hg SE 2 19 However the difference is not significant 0 7 > P > 0 6

In our experimental series *there was no correlation between Po in the an terior chamber and the administered dose of* urethan and thiopental sodium or the time interval from the administration of the named substances until the chamber was punctured All P values were > 0 5

There was no correlation between the Po in the aqueous humour and in the arterial blood (0 95 > P > 0 8) and in the named experimental set up the Po *in arterial blood was rather unstable The explanation is possibly that in a* rabbit in the supine position there may be badly ventilated and perfused lung segments and this may lead to marked fluctuations in the oxygen tension of the arterial blood That the rabbits were otherwise satisfactorily ventilated is apparent from the more constant Pco

No correlation was found between the Po in the anterior chamber and the Pco (0 1 > P > 0 05) and pH in arterial blood (0 7 > P > 0 6)

Perhaps the lacking correlation between the oxygen tension in the arterial blood and in the aqueous humour is explicable as follows In the rabbit about one per cent of the aqueous humour is exchanged per minute whereas the blood *volume of the eye is* exchanged about 50 times a minute (Trokel 1966) Thus between these exchanges there is a factor of 1 2500 Within *the approx* 45 seconds which made up the reading time it must be presumed that the oxygen diffusion across the blood/aqueous barrier could not have time to manifest itself at the prevalent Po gradients

Summary

Measurements *of the oxygen* tension in the aqueous humour were carried out using a Beckman microelectrode *inserted into the* anterior chamber of 19 rab bits under urethan and thiopental sodium anaesthesia

In 15 eyes the mean value was 30 5 mm Hg SD 11 71 (3 C 60 mm Hg)

logical saline (Drenckhahn & Lorenzen) and the protein content low (0 02%) (Adler)

The greatest disadvantage of using the Beckman microelectrode is the inevitable loss of aqueous humour in connection with the puncture and during the measurement Therefore the value read must be influenced by the secondary aqueous as well as the fluid in the posterior chamber The needle was inserted centrally just in front of the pupil but during the evacuation of the aqueous humour occasional contact between the electrode and the solid structures of the eye cannot be ruled out and this changes the conditions for passage of oxygen across the membrane as well as the calibration

Bleeding in the chamber must be avoided and so must introduction of air Moreover the electrode must not be moved as this will cause elevated values as also observed by Drenckhahn & Lorenzen (1958)

The measurement of the temperature in the anterior chamber was performed with open as well as with closed eyes No eyelid speculum was used and during the measurement of the Po the cornea was either exposed or almost covered by the eyelids depending upon the depth of anaesthesia

Fig 2 shows that there is a marked dispersion of the oxygen tension levels in the anterior chamber The results as apparent from Table I are not directly comparable as different measuring methods and varying statements of temperature have been used It is common to all that the measurements have been done on eyes exposed to puncture and therefore the composition of the aqueous during the study period is varying

We tried to measure the oxygen tens on in aqueous humour drawn by punc

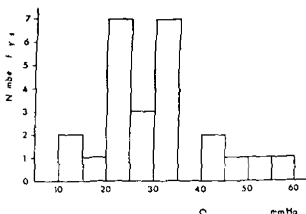


Fig 2
The abscissa represents a range of tension rising in steps of 5 mmHg and starting at 10–15 mmHg

ACTA OPHTHALMOLOGICA VOL. 49 1971

From the University Institute of Forensic Medicine
(Head: Professor H. Gormsen, M.D.)
Copenhagen, Denmark

PENETRATION RATE OF ALCOHOL INTO THE VITREOUS HUMOR STUDIED WITH A NEW IN VIVO TECHNIQUE

BY

JENS ERLAND OLSEN

Forensic studies of the vitreous humor have stated that this fluid is very suitable for alcohol determinations (2, 3, 6). The forensic significance of determining the post mortem alcohol concentration in blood is well known. Especially in cases of putrefaction a post mortem formation of alcohol in blood is sometimes seen from the action of yeasts and bacteria. Comparative studies of post mortem ethyl alcohol concentrations in blood and vitreous humor (5) have rendered it possible to decide whether the alcohol in a dead body should be considered the result of post mortem formation, since this phenomenon was never observed in the vitreous humor, which is seldom contaminated and contains rather small amounts of sugar and protein.

In agreement with the presumption that alcohol is evenly distributed throughout the body fluids by diffusion, the ratio of blood and vitreous alcohol concentrations (ratio $_{VH}$) was found to be 0.73 in human bodies. Calculated from the normal water content of these fluids (*blood 78 per cent, vitreous humor 99 per cent*) a ratio $_{VH}$ of 0.79 was to be expected. The difference found was attributed to the higher dry matter content of post mortem blood due to the hemoconcentration so often seen in cases of poisoning. Sometimes the ratio $_{VH}$ found was significantly higher than 0.79 when death had occurred before dif-

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The electrode is temperature sensitive and the investigations were therefore supplemented by measurements of the temperature in the anterior chamber (35° 7 C) The Po_2 mean value corrected for temperature was 32 mm Hg and differed by a maximum of 5 per cent from the directly read value There was no correlation between the Po in the aqueous humour the anaesthetic method used or the Po in the arterial blood

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From the University Institute of Forensic Medicine
(Head Professor H Gormsen M D)
Copenhagen Denmark

PENETRATION RATE OF ALCOHOL INTO THE VITREOUS HUMOR STUDIED WITH A NEW *IN VIVO* TECHNIQUE

BY

JENS ERLAND OLSEN

Forensic studies of the vitreous humor have stated that this fluid is very suitable for alcohol determinations (2 3 6) The forensic significance of determining the post mortem alcohol concentration in blood is well known Especially in cases of putrefaction a post mortem formation of alcohol in blood is sometimes seen *from the action of yeasts and bacteria Comparative studies of post mortem* ethyl alcohol concentrations in blood and vitreous humor (5) have rendered it possible to decide whether the alcohol in a dead body should be considered the result of post mortem formation since this phenomenon was never observed in the vitreous humor which is seldom contaminated and contains rather small amounts of sugar and protein

In agreement with the presumption that alcohol is evenly distributed throughout the body fluids by diffusion the ratio of blood and vitreous alcohol concentrations (ratio $_{B/V}$) was found to be 0 73 in human bodies Calculated from the normal water content of these fluids (blood 78 per cent vitreous humor 99 per cent) a ratio $_{B/V}$ of 0 79 was to be expected The difference found was attributed to the higher dry matter content of post mortem blood due to the hemoconcentration so often seen in cases of poisoning Sometimes the ratio $_{B/V}$ found was significantly higher than 0 79 when death had occurred before dif

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fusion equilibrium was attained i e during the process of absorption provided that a post mortem formation of alcohol could be excluded

During the aforesaid investigations (2 5) it was considered of interest to study the variation in ratio v/c with time in order to estimate if possible the time of alcohol intake and death in human cadavers Penetration studies of alcohol have been performed *by others (1 4)* and the primary purpose of presenting this paper has been to demonstrate a new *in vivo* technique making it possible to follow the penetration of alcohol into the vitreous humor of the eye apparently without disturbing the physiological processes

Technique

An albino rabbit was anaesthetised with barbiturate through the ear vein Fifteen minutes later ethyl alcohol (3 g/kg body weight) was injected in the abdominal cavity and a plastic catheter for blood sampling was inserted in a femoral artery A sterile needle (Steristar 19 G × 1½) equipped with a rubber membrane was inserted in the vitreous humor by lateral puncture of the ocular bulb (Fig 1) Looking through the pupil of the rabbit it was possible to place the point of the needle in the center of the eyeball Finally the needle was fixed to the apparatus holding the head of the rabbit

The *vitreous samples* were obtained by means of a Hamilton syringe (Model 701–NCN) the needle of which was inserted through the rubber membrane of the Steristar needle 4 microlitres of vitreous humor were aspirated per analysis and immediately injected into the gas chromatograph (F & M model 700 with flame ionization detector 14 % Carbowax on Diatoport S 60–80 Mesh) By means of the gas chromatograph the volatile compounds in a very small amount

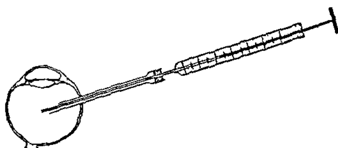
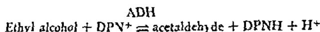


Fig 1

Schematic drawing of a Hamilton syringe (Model 701–NCH) inserted in the eye through a permanent intra ocular Steristar needle (No 19 G × 1½) which has been tightened with a rubber membrane (cf text)

of liquid (4 microlitres) are transferred to gaseous form and separated in a column from which they emerge each at a specific time (the retention time) Each compound is registered graphically by a curve the height of the curve top being a measure of the concentration In this way the vitreous alcohol concentration was known 2 minutes after the sampling In one experiment 4 samples from each eye were obtained before the rabbit was killed

The alcohol concentrations of the simultaneously removed blood samples were determined by the specific enzymatic ADH method The principles employed in this method are the ability of alcohol dehydrogenase (ADH) to catalyze the dehydrogenation of alcohol to aldehyde in the presence of the coenzyme diphophopyridine nucleotide (DPN)



$$\text{Ethyl alcohol} + DPN^{+} \overset{ADH}{\rightleftharpoons} \text{acetaldehyde} + DPNH + H^{+}$$

The amount of DPNH is determined spectrophotometrically by means of the light absorption at 340 mμ thus providing a measure of the alcohol amount present

Results

The alcohol concentrations in blood an vitreous humor in relation to time are shown in Fig 2 together with the variation in ratio$_{V/B}$ As expected the alcohol concentration of the blood showed an almost linear fall The vitreous alcohol concentration showed a linear rise until equilibrium was attained after 210 minutes (i e ratio$_{V/B}$ = 0.93) After this time the concentrations showed a parallel fall

Apparently this technique does not interfere with the physiologic processes concerning the diffusion of alcohol from the blood to the vitreous humor and vice versa.

That this presumption is true was shown by treating nine rabbits in the same way as controls except that the vitreous humor was removed in toto by ordinary puncture at different times (t 0 to 300 minutes) In each of these nine cases the ratio$_{V/B}$ almost exactly corresponded to the curve shown in Fig 2

Summary

A new technique for in vivo studies of the penetration of alcohol into the vitreous humor is described The technique renders it possible to remove repeated samples of 4 microlitres each of vitreous humor from the same eye by means

fusion equilibrium was attained i e during the process of absorption provided that a post mortem formation of alcohol could be excluded

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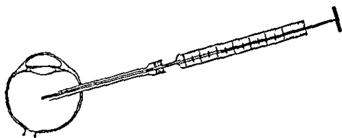


Fig 1
Schematic drawing of a Hamilton syringe (Model 701-NCH) inserted in the eye through a permanent intra ocular Steristar needle (No 19 C × 1½) which has been tightened with a rubber membrane (cf text)

From the University of Bergen School of Medicine
D partment of Ophthalmolcgy
(Head Professor Torstein I Bertelsen M D)

THE FREQUENCY OF OPTIC NERVE DAMAGE AND SURGICAL TREATMENT IN CHRONIC SIMPLE GLAUCOMA AND CAPSULAR GLAUCOMA

BY

HENRY AASVED

Key words Chronic simple glaucoma Capsular glaucoma Optic nerve damage Surgical treatment

There are many points of similarity between chronic simple glaucoma and cap sular glaucoma (open angle glaucoma associated with fibrillopathia epithelio capsularis the so called senile exfoliation or pseudoexfoliation) Both of them are of the open angle type In the early stages there is only moderate elevation of the intraocular pressure and the diseases progress slowly They are usually treated in the same manner

However apart from the presence of fibrillopathy capsular glaucoma seems to differ from simple glaucoma in other ways Numerous authors have described an increased spread of pigmentation in capsular glaucoma and it has been asserted that the pigmentation in the chamber angle has a special pattern char acteristic of this disease (Sampaolesi 1960)

It has also been claimed that capsular glaucoma is more difficult to control by medication that patients with this disease more often require surgical treat

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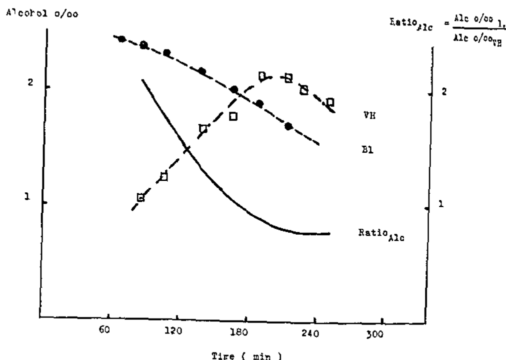


Fig 2
Ethyl alcohol concentration (g/1000 ml) in vitreous humor (VH) and blood (Bl) in a rabbit (weight 3 2 kg) after an intraperitoneal injection of 8 1 g ethyl alcohol at zero time

of a permanent needle The vitreous humor obtained in this way is directly fitted for gas chromatographic alcohol determination

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The out patient group consisting of 97 patients treated at the out patient clinic of the Department of Ophthalmology University of Bergen, from the opening of the Department on September 5 1961 to January 1 1969 Simple glaucoma was found in 67 of these patients and capsular glaucoma in 30

This group does not include patients from the mass screening or cases which had earlier been in patients Otherwise it embraces all the out patients in the above mentioned period. Tonometry is here carried out as a routine measure on all patients above the age of 40 unless there are special contraindications.

The in patient group consisting of all 277 patients admitted to the Department of Ophthalmology the University of Bergen, with simple or capsular glaucoma from the opening of the Department on September 5 1961 to January 1 1969 Of these patients 164 had simple glaucoma 110 capsular glaucoma and 3 bilateral glaucoma associated with unilateral fibrillopathy In the case of these three patients the glaucoma associated with fibrillopathy was registered as a capsular type and the glaucoma in the fellow eye as a simple glaucoma. This group of patients consists mainly of patients in whom the intraocular pressure could not be satisfactorily controlled by ambulant treatment.

The in patient group includes 33 patients from the mass screening and out patient groups who were admitted to the ophthalmological department during the above mentioned period for glaucoma. Among these there were 19 patients (35 eyes) with simple glaucoma and 14 patients (23 eyes) with capsular glaucoma Corrections have been made for this duplicate registration in calculating the total number examined

The total material thus consists of 444 patients 298 with simple glaucoma 143 with capsular glaucoma and 3 with capsular glaucoma in one eye and simple glaucoma in the other eye.

If fibrillopathy was not observed with pupils at normal size the examination was repeated after dilatation with homatropin or cyclopentolate hydrochloride (Cyclogyl®)

The same medical treatment has been employed in the two types of glaucoma (pilocarpin or Mintacol® if necessary supplemented by adrenalin and/or acetazolamid)

Optic nerve damage was registered when the optic disc was excavated to the edge and/or visual field defects characteristic of glaucoma were demonstrated In 21 eyes the state of the optic nerve could not be assessed

The comparison between the two types of glaucoma with respect to the frequency of surgical treatment refers only to the in patient group

Surgical treatment has been employed when the intraocular pressure could not be satisfactorily controlled by maximal medication in the clinic The indications were the same in both types of glaucoma

No eyes were registered more than once even if more than one operation had been performed Enucleation in absolute glaucoma has not been considered as an operation for glaucoma

The frequency of optic nerve damage and surgical treatment has been calculated on the basis of the number of glaucomatous eyes

In correcting for differences in age distribution in the different patient groups the indirect method (Hill 1961) was used the total material being taken as standard

The number of glaucomatous eyes in each patient group and in the total material appears from Table I which also shows the age distribution

ment and that the prognosis is poorer than in simple glaucoma (Vogt 1930 Grzedzielski 1931 Blaickner 1932 Gradle & Sugar 1947 Joannides et al 1961 Gillies 1962, Tarkkanen 1965, Horven I 1966 Klouman 1967)

The aim of this study is to compare the two types of glaucoma with respect to the frequency of optic nerve damage and surgical treatment

The comparison is made on the basis of 3 groups of patients collected from mass screening from an out patients clinic and from an eye department It must be expected that the 3 groups will on the average represent varying degrees of severity of glaucoma the cases found in the course of mass screening being those most lightly affected the patients from the eye department being most seriously affected and the out patient group being an intermediate category If the two types of glaucoma have the same clinical course the frequency of optic nerve damage within each of the three patient groups will be the same in simple glaucoma and capsular glaucoma and the need for surgical treatment will be the same in both types

Consistent deviations between the two types of glaucoma would however be an indication that simple glaucoma and capsular glaucoma have different prognoses

Material and Methods

The material was collected in Bergen Norway and consists of persons above the age of 50 with simple glaucoma or capsular glaucoma The material is the same as that used in the investigation of the frequency of fibrillopathy among patients with open angle glaucoma (Aasved) The same work lists the criteria used for the diagnosis of glaucoma

Capsular glaucoma was registered when fibrillopathy was found in an eye with chronic open angle glaucoma and there was no anamnestic information or other findings that might explain the pathological increase in intraocular pressure

Simple glaucoma was registered when fibrillopathy was not demonstrated in otherwise similar conditions

The investigation is based on the following three groups of patients

The mass screening group consisting of 103 newly diagnosed cases discovered during mass screening at 53 different industrial concerns and 50 different old people s homes in Bergen Among these simple glaucoma was found in 86 patients and capsular glaucoma in 17 The investigation embraced 5 446 persons above the age of 50 in whom there were no previous findings of glaucoma or other conditions capable of influencing the intraocular pressure or preventing a proper assessment of the anterior surface of the lens

Results

For each type of glaucoma the frequency of optic nerve damage was approximately the same in men and in women ($P > 0.50$). The difference in the distribution of the two sexes in the groups of patients thus appears to be without significance. The two sexes have therefore been presented together in the tables and analyses.

Table II shows the frequency of optic nerve damage in the two glaucoma types in the total material. In both types of glaucoma an increasing frequency of optic nerve damage was found on increasing age. The two deviations from this general trend are assumed to be due to the relatively small number of eyes in the groups concerned.

The table shows that optic nerve damage occurred far more often in eyes with capsular glaucoma (74.0 per cent) than in eyes with simple glaucoma (45.5 per cent). This difference has not arisen by chance ($P < 0.0005$). It appears in all age groups and is therefore not substantially altered by statistical correction for age. Even in the youngest group the frequency was more than 60 per cent in capsular glaucoma, whereas the highest frequency in simple glaucoma was 59.5 per cent – in the age groups 70–79 years.

Table III shows the frequency of optic nerve damage in simple glaucoma and capsular glaucoma in the three patient groups. The lowest total frequency of optic nerve damage was observed among the eyes in the mass screening group (25.4 per cent), the frequency being considerably higher in the out patient group (51.8 per cent) and higher still in the in patient group (67.3 per cent). This variation between the groups has not occurred by chance ($P < 0.0005$) and was not substantially altered by correction for a somewhat varying age distribution in the patient groups.

The frequency of optic nerve damage in simple glaucoma and capsular glaucoma was about the same in the mass screening group ($P = 0.70$). In the two other patient groups optic nerve damage was definitely more common in eyes with capsular glaucoma than in eyes with simple glaucoma. The difference has not arisen by chance either in the out patient group ($P < 0.05$) or the in patient group ($P < 0.005$). The difference between the two glaucoma types was evident in all age groups, which explains why the correction for age resulted in only minor changes.

In the 33 patients who were admitted to the Department of Ophthalmology from the mass screening or the out patient group there was optic nerve damage in 23 of 35 eyes with simple glaucoma (66 per cent) and in 17 of 23 eyes with capsular glaucoma (74 per cent). These patients thus showed the same general pattern as the whole of the in patient group.

Table IV shows the frequency of surgical treatment in the in patient group. Here also the frequency for each type of glaucoma was very nearly the same in

Table 1

Age distribution in different groups of glaucomatous eyes In the column marked total correction has been made for double registration of 35 eyes with simple glaucoma and 23 eyes with capsular glaucoma

Age (years)	Mass screening		Out patients		In patients		Total	
	No eyes	per cent	No eyes	per cent	No eyes	per cent	No eyes	per cent
Simple glaucoma								
50–59	50	32 5	27	23 1	42	13 9	117	21 7
60–69	66	42 9	48	41 0	115	38 1	207	38 5
70–79	17	11 0	29	24 8	120	39 7	158	29 4
80–89	21	13 6	13	11 1	25	8 3	56	10 4
Total	154	100 0	117	100 0	302	100 0	538	100 0
Capsular glaucoma								
50–59	3	13 0	3	6 1	10	5 2	13	5 4
60–69	8	34 8	23	46 9	36	18 6	57	23 6
70–79	5	21 8	14	28 6	104	53 9	116	47 9
80–89	7	30 4	9	18 4	43	22 3	56	23 1
Total	23	100 0	49	100 0	193	100 0	242	100 0
Total								
50–59	53	30 0	30	18 1	52	10.5	130	16 7
60–69	74	41 8	71	42 8	151	30 5	264	33 8
70–79	22	12 4	43	25 9	224	45 3	274	35 1
80–89	28	15 8	22	13 2	68	13 7	112	14 4
Total	17[illegible]	100 0	16[illegible]	100 0	[illegible]	100 0	780	100 0

For each type of glaucoma the frequency of optic nerve damage was approximately the same in men and in women ($P > 0.50$). The difference in the distribution of the two sexes in the groups of patients thus appears to be without significance. The two sexes have therefore been presented together in the tables and analyses.

Table II shows the frequency of optic nerve damage in the two glaucoma types in the total material. In both types of glaucoma an increasing frequency of optic nerve damage was found on increasing age. The two deviations from this general trend are assumed to be due to the relatively small number of eyes in the groups concerned.

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The frequency of optic nerve damage in simple glaucoma and capsular glaucoma was about the same in the mass screening group ($P = 0.70$). In the two other patient groups optic nerve damage was definitely more common in eyes with capsular glaucoma than in eyes with simple glaucoma. The difference has not arisen by chance either in the out patient group ($P < 0.05$) or the in patient group ($P < 0.005$). The difference between the two glaucoma types was evident in all age groups, which explains why the correction for age resulted in only minor changes.

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Table IV shows the frequency of surgical treatment in the in patient group. Here also the frequency for each type of glaucoma was very nearly the same in

Table II

Frequency of optic nerve damage in eyes with simple glaucoma and capsular glaucoma in the total material

Age (years)	Simple glaucoma			Capsular glaucoma			Total		
	Total No eyes	With damage No eyes	With damage per cent	Total No eyes	With damage No eyes	With damage per cent	Total No eyes	With damage No eyes	With damage per cent
50–59	117	36	30 8	13	9	69 2	130	45	34 6
60–69	207	88	42 5	57	36	63 2	264	124	47 0
70–79	158	94	59 5	116	90	77 6	274	184	67 1
80–89	56	27	48 2	56	44	78 6	112	71	63 4
Total	538	245	45 5	242	179	74 0	780	424	54 4
Age corrected frequencies			47 8			67 3			

Table III

Fre juency of optic nerve damage in eyes with simple glaucoma and capsular glaucoma in d fferent groups of ; atients

Type of glaucoma	Mass screening			Out ; atients			In patients		
	Total No eyes	With damage No eyes	With damage per cent	Total No eyes	With damage No eyes	With damage per cent	Total No eyes	With damage No eyes	With damage per cent
Simple glaucoma	154	40	26 0	117	5[illegible]	44 4	302	176	58 3
Capsular glaucoma	23	5	21 7	49	34	69 4	193	157	81 3
Total	177	45	25 4	166	86	51 8	495	333	67 3

Table IV

Frequency of surgical anti glaucoma treatment in eyes with simple glaucoma and capsular glaucoma

Age (years)	Simple glaucoma			Capsular glaucoma			Total		
	Total	Operation		Total	Operation		Total	Operation	
	No eyes	No eyes	per cent	No eyes	No eyes	per cent	No eyes	No eyes	per cent
50–59	42	15	35 7	10	4	40 0	52	19	36 5
60–69	115	24	20 9	36	13	36 1	151	37	24 5
70–79	120	19	15 8	104	39	37 5	224	58	25 9
80–89	25	7	28 0	43	13	30 2	68	20	29 4
Total	302	65	21 5	193	69	35 8	495	134	27 1
Age corrected frequencies			21 5			36 2			

both men and women For this reason *the two sexes have been presented* collectively

No consistent variation of the frequency of surgical treatment was *found on increasing age*

The frequency of surgical treatment was considerably higher in eyes with capsular glaucoma (35 8 per cent) than in eyes *with simple glaucoma* (21 5 per cent) The difference *between the two types* of glaucoma has not arisen by chance ($P < 0\ 005$) It was apparent in all age groups and was not altered by *correction for slight variations in* age distribution In this correction all glaucomatous eyes on which surgical treatment had been performed were used as standard

Calculation of the frequency of surgical treatment on the basis of the number of patients accentuates the difference between the two types of glaucoma Operations had been performed on 40 of the 164 patients with simple glaucoma (24 4 per cent) compared with 49 of the 110 patients with capsular glaucoma (44 5 per cent)

The two types of glaucoma also differed with respect to the development of absolute glaucoma Table V shows the frequency of absolute or nearly absolute glaucoma in some earlier materials and in the present study In all materials the frequency is higher in capsular glaucoma than in simple glaucoma. In *the present study the difference* has not arisen by chance ($P < 0\ 0005$)

Comments

As a natural consequence of the selection of patients in this study there was an increase in the frequency of optic nerve damage *from patient group to pa*

Table V
Incidence of absolute (or nearly absolute) glaucoma in simple glaucoma and capsular glaucoma.

Author Year	Simple glaucoma			Capsular glaucoma		
	Total No	Absolute glaucoma No	Absolute glaucoma per cent	Total No	Absolute glaucoma No	Absolute glaucoma per cent
Tarkkanen 1965	45 eyes	8	18	45 eyes	13	29
Hansen 1 1966	1 6 eyes		4 0	44 eyes		15 9
Klouman 1967	1?? pat.	9	7.3	199 pat.	57	28 6
Present study	302 eyes	11	3 6	193 eyes	31	16 1

tient group in this order mass screening group out patient group in patient group In the present study the comparison of the two types of glaucoma has been made on the basis of these three patient groups, and by classification according to age Tarkkanen (1965) compared the two types of glaucoma in 45 patients with bilateral glaucoma associated with only unilateral fibrillopathy In Hörven s material (1966) the comparison was made after classification according to the time which had elapsed from the diagnosis of glaucoma until the study was carried out

The results of former investigations and of the present study show the same tendency

As expected there was an increasing frequency of optic nerve damage with increasing age in both types of glaucoma In comparing the two types of glaucoma correction should therefore be made for variations in age distribution.

A markedly higher frequency of optic nerve damage was demonstrated in capsular glaucoma than in simple glaucoma

It is notable that even the highest age group of eyes with simple glaucoma had a lower frequency of optic nerve damage than the youngest age group of eyes with capsular glaucoma

The difference between the two types of glaucoma did not reveal itself to the same degree in the three patient groups In the mass screening group approximately the same frequency of optic nerve damage was found in simple glaucoma as in capsular glaucoma The explanation of this may be that many of the cases discovered by chance during a mass screening *will* have an early stage of glaucoma Any difference in clinical course that may be present between the two types of glaucoma will therefore not be evident in a patient group collected by mass screening The two other patient groups represent a comparatively greater number of advanced cases of glaucoma In both these groups a higher frequency of optic nerve damage was found in capsular glaucoma than in simple glaucoma (Table III)

The increase in frequency of optic nerve damage from the mass screening group to the other groups was thus markedly greater in capsular glaucoma than in simple glaucoma

It is also of great interest that there is a considerably higher frequency of absolute or nearly absolute glaucoma in capsular glaucoma than in simple glaucoma (Table V)

In the in patient group surgical treatment was necessary 1 7 times as *often* in capsular glaucoma as in simple glaucoma (Table IV)

This study confirms the assumption that capsular glaucoma is a more intractable form of glaucoma than simple glaucoma

The difference in the clinical course of the two types of glaucoma is of great

importance in the comparison of the frequency of fibrillopathy in different glaucoma materials In consequence of the more serious clinical course the relative incidence of capsular glaucoma in the present study increased from group to group in the same sequence as the average severity of glaucoma The frequency of fibrillopathy in the glaucoma materials has been assessed in another work by the present author (Aasved)

Summary

The clinical course in chronic simple glaucoma and capsular glaucoma has been assessed on the basis of the incidence of optic nerve damage and the number of cases which had received surgical treatment for glaucoma

The material comprises three different patient groups in which the frequency of optic nerve damage increased in this order mass screening group (25 4 per cent) out patient group (51 8 per cent) and in patient group (67 3 per cent)

The frequency in optic nerve damage in simple glaucoma and capsular glaucoma was about the same in the mass screening group In the out patient and in patient groups optic nerve damage was definitely more common in capsular glaucoma than in simple glaucoma. In the material as a whole optic nerve damage was markedly more frequent in capsular glaucoma (74 0 per cent) than in simple glaucoma (45 5 per cent)

Surgical treatment for glaucoma was carried out more often in capsular glaucoma (35 8 per cent) than in simple glaucoma (21 5 per cent)

A higher frequency of eyes with absolute or nearly absolute glaucoma was found in capsular glaucoma (16 1 per cent) than in simple glaucoma (3 6 per cent)

The results indicate that capsular glaucoma has a more serious clinical course and is a more serious type of glaucoma than simple glaucoma

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From the University of Bergen School of Medicine
Department of Ophthalmology
(Head Professor Torstein I Bertelsen M D)

INTRAOCULAR PRESSURE IN EYES WITH AND WITHOUT FIBRILLOPATHIA EPITHELIOCAPSULARIS

(so called senile exfoliation or pseudoexfoliation)

BY

HENRY AASVED

Key words Fibrillopathy Exfoliation or pseudoexfoliation of the anterior lens capsule. Intraocular pressure Capsular glaucoma.

The main object of the present study is to compare the intraocular pressure in eyes with and without fibrillopathia epitheliocapsularis (so called senile exfoliation or pseudoexfoliation of the anterior lens capsule)

The relationship between fibrillopathy and the intraocular pressure has chiefly been studied by investigating the frequency of glaucoma in patients with fibrillopathy In earlier materials this frequency has varied from 0 per cent (Hollows & Graham 1966) to 100 per cent (Bhaduri 1949 Holm Pedersen 1954 Simon 1961) The average is probably about 50 per cent (cf tabular surveys of most earlier investigations by Leydhecker 1960 and Tarkkanen 1962)

In the present study a comparison of the intraocular pressure in eyes with and without fibrillopathy has been based on mass screening for glaucoma and fibrillopathy in the general population The material also forms the basis of a study of the frequency of glaucoma among persons with and without fibrillopathy In this connection it is of interest to ascertain whether patients with capsular

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glaucoma represent a particularly elevated section of the distribution curve for intraocular pressure or whether there is an even transition from the normal variation sector to pathological levels of intraocular pressure, as in the population at large.

The question of whether the intraocular pressure in eyes with fibrillopathy alters with time is of general practical interest. It has been claimed that "if you find exfoliation of the lens capsule and the tension is low normal that patient is going to be on your list for the rest of his life" (Chandler 1959). The present author has evaluated this problem in the course of a follow-up study covering a period of 6–7 years of the intraocular pressure in eyes with fibrillopathy.

The relationship between fibrillopathy and glaucoma is discussed against the background of this and former studies.

Material and Methods

The material was collected in 1962–63 by a mass screening at 85 industrial concerns and 30 old people's homes in Bergen, Norway, and is more closely described in another publication by the present author (Aasved).

The material embraces 8 537 persons above the age of 40 (17 074 eyes). In this material fibrillopathy was found in 75 persons (107 eyes). These form the foundation for the evaluation of the intraocular pressure in eyes with fibrillopathy. The intraocular pressure in eyes without fibrillopathy was evaluated on the basis of the 8 462 persons without fibrillopathy. The fellow eyes of persons with unilateral fibrillopathy were not included in this group.

The intraocular pressure was measured by means of a standardized Schiøtz weight tonometer with the subject in a recumbent position. The same tonometer was used throughout the mass screening project. The anaesthetic used was Oxibuprocain 0.4 per cent (Novesin®). The calibration scale of 1955 was used on converting to mm Hg.

The diagnosis open angle glaucoma was based on examinations made during the first few months following the initial screening. When increased intraocular pressure was not combined with excavation of the optic discs to the edge and/or visual field defects characteristic of glaucoma, the following criteria were employed:

	Normal	Borderline	Glaucoma
Intraocular pressure	≦ 20 mm Hg	21–24 mm Hg	≧ 25 mm Hg
Water drinking test increase of i.o.p.	≦ 6 mm Hg	7–9 mm Hg	≧ 10 mm Hg
Outflow facility mm^3/minute/mm Hg	≧ 0.19	0.18–0.13	≦ 0.12

In the course of the follow up of a group of persons with fibrillopathy the intraocular pressure was measured at intervals for a period of 6 to 7 years

Fourteen persons in whom the present author was able to measure the intra ocular pressure before and after the development of fibrillopathy are discussed

In the electronic processing of the data the Welsh Sverdrup modified t test of two mean values with possibly disparate variants was employed in comparing the intraocular pressure in the different groups

The results showed the same tendency in both men and women The two sexes were therefore presented together for the sake of clarity

Results

Table I shows the average intraocular pressure in eyes with and without fibrillopathy in the different age groups *The one person in the group* 90–99 years with bilateral *fibrillopathy had intraocular pressure of* 6 5/5 5 and 6 0/5 5 (Schiotz) In the other age groups the average intraocular pressure in eyes with fibrillopathy varied between 16 43 mm Hg and 18 75 mm Hg The average intraocular pressure in all eyes with fibrillopathy was 17.50 mm Hg

In eyes without fibrillopathy the average intraocular pressure varied from 14 12 mm Hg to 14 65 mm Hg the overall average being 14.50 mm Hg

The average intraocular pressure in eyes with fibrillopathy was thus 3 mm Hg

Table I

Average intraocular pressure in eyes with and without fibrillopathy

Age (years)	With fibrillopathy			Without fibrillopathy		
	No eyes	Intraocular pressure average mm Hg	standard deviation	No eyes	Intraocular pressure average mm Hg	standard deviation
40–49	0	-	-	618	14.37	2 40
50–59	17	16 74	3 05	5634	14.56	2 65
60–69	9	18 10	4.30	3672	14 64	3 09
70–79	30	18 75	11 00	906	14 41	3 17
80–89	35	16 43	5 15	538	14 65	3 51
90–99	2	14 00	0 60	42	14 12	2.53
Total	107	17.50	07	169 4	14.50	2 73

higher than that in eyes without fibrillopathy This difference has not occurred by chance (P < 0 001)

The exclusion of glaucomatous eyes from both groups resulted in some reduction of this difference but the average intraocular pressure in eyes with fibrillopathy remained higher than in eyes without fibrillopathy respectively 15 5 mm Hg and 14 4 mm Hg

No consistent alteration of the intraocular pressure with increasing age was found either in eyes with or without fibrillopathy

Fig 1 shows the distribution of the intraocular pressure in eyes with and without fibrillopathy In both groups the curve shows a somewhat skew distribution with more persons in the high pressure sector than would be expected in a normal (Gaussian) distribution For eyes without fibrillopathy the curve shows the same path as in comparable earlier studies (Leydhecker et al 1959 Bertelsen et al 1965) In eyes with fibrillopathy this skew distribution is more pronounced and the whole curve shows a shift towards a higher intraocular pressure The most frequent scale reading in eyes without fibrillopathy was 6 0/5 5 (corresponding to 14 6 mm Hg) whereas in eyes with fibrillopathy it was 5 0/5 5 (corresponding to 17 3 mm Hg)

In 43 persons with unilateral fibrillopathy the average intraocular pressure was 16 53 mm Hg (S D 3 57) in the affected eyes and 14 88 mm Hg (S D 2 90) in the unaffected eyes This difference is on the border of statistical significance (P = 0 05)

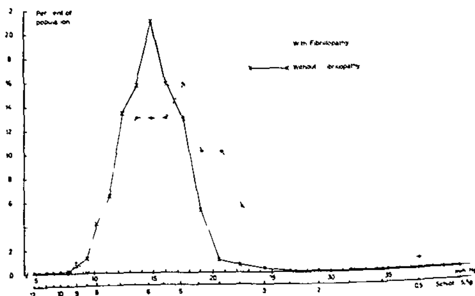


Fig 1

The distribution of the intraocular pressure in eyes with and without fibrillopathy

The difference between the average intraocular pressure in the affected eyes in unilateral cases and in the total number of eyes with fibrillopathy may have occurred by chance ($P > 0.05$) as may also the difference between the fellow eyes in unilateral cases and the total number of eyes without fibrillopathy ($P > 0.05$)

The relationship between the intraocular pressure in affected and unaffected eyes in the 43 persons with unilateral fibrillopathy is shown in *Fig* 2 In 28 persons the intraocular pressure was higher in the affected eye than in the fellow eye In 13 persons the intraocular pressure was the same in both eyes whereas 2 persons had lower pressure in the eye with fibrillopathy By way of comparison it may be mentioned that 14 of the 32 bilateral cases had disparate intraocular pressure in the two eyes

The relationship between fibrillopathy and intraocular pressure also appears from Table II which shows the frequency of fibrillopathy at the different pressure levels At intraocular pressures of 5 5/5 5 and lower there were only small *variations in frequency With increasing intraocular* pressures the frequency of fibrillopathy increased reaching 7 2 per cent at intraocular pressures of 3 0/5 5 and above

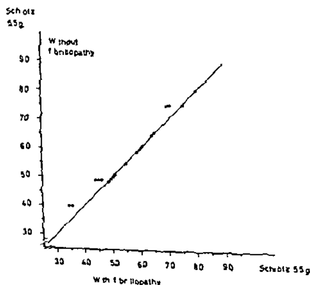


Fig 2

Correlation of the intraocular pressure in the two eyes in 43 persons with unilateral fibrillopathy The 15 dots along the line represent persons with equal i o p in the two eyes

Table II

Frequency of fibrillopathy at different levels of intraocular pressure

Intraocular pressure Schiotz 5.5 g	Total No. eyes	With fibrillopathy No. eyes	With fibrillopathy per cent
0.0– 3.0	97	7	7.2
3.5– 4.0	300	17	5.7
4.5– 5.0	3136	28	0.9
5.5– 6.0	6315	28	0.4
6.5– 7.0	4986	23	0.5
7.5– 8.0	1833	3	0.2
8.5– 9.0	338	1	0.3
9.5–10.0	64	0	0
10.5–12.0	5	0	0
Total	17074	107	0.6

The frequency of open angle glaucoma can be seen from Table III. The frequency among all persons with fibrillopathy was 22.7 per cent and was thus far higher than among persons without fibrillopathy (1.2 per cent). This difference has not occurred by chance ($P < 0.001$). The table also shows that an increase in the frequency of glaucoma with increasing age such as that found in persons

Table III

Frequency of open angle glaucoma among persons with and without fibrillopathy

Age (years)	With fibrillopathy			Without fibrillopathy		
	Total No. persons	With glaucoma No. persons	With glaucoma per cent	Total No. persons	With glaucoma No. persons	With glaucoma per cent
40–49	0	0	–	3091	16	0.5
50–59	10	3	30.0	2817	30	1.1
60–69	18	5	27.8	1811	36	2.0
70–79	23	4	17.4	453	9	2.0
80–89	23	5	21.7	269	11	4.1
90–99	1	0	–	21	0	–
Total	[illegible]	17	22.7	8462	[illegible]	1.2

without fibrillopathy was not found in persons with fibrillopathy The frequency of glaucoma was somewhat higher among persons with bilateral fibrillopathy (9 of 32 persons) than among persons with unilateral fibrillopathy (8 of 43 persons) This difference may however have occurred by chance ($P > 0.5$)

In the whole material there were also 9 cases of narrow angle glaucoma none of them with fibrillopathy

Follow up Study

Of the 75 persons with fibrillopathy found on mass screening 27 are dead and were not followed up after 1965 For various reasons 10 other persons have not been followed up since 1963 In the remaining 38 persons the intraocular pressure was followed up for for 6–7 years Of these 13 persons had capsular glaucoma at the time of the mass screening

In 2 of the 6 persons initially registered as borderline cases the intraocular pressure has since risen to pathological levels the pressure remaining unchanged in the other 4

In the remaining 19 persons (26 eyes with fibrillopathy) no suspicion of glaucoma was found in the course of mass screening During the follow up period an increase in intraocular pressure was demonstrated in only 1 of these (an increase of approx 12 mm Hg in one eye) In the other 18 persons the intraocular pressure has remained unchanged throughout the whole follow up period

The author has observed the development of fibrillopathy in 14 persons (14 eyes) being followed up for various reasons In these eyes the intraocular pressure had remained on the same level for several measurements before fibrillopathy was demonstrated In 6 of these eyes (43 per cent) the appearance of fibrillopathy was accompanied or closely followed by an increase in intraocular pressure varying from 4 to 12 mm Hg In the other 8 eyes intraocular pressure remained unchanged after the development of fibrillopathy

Comments

The present study has demonstrated that *the intraocular pressure in eyes with fibrillopathy is higher on the average than in eyes without fibrillopathy* This applies even if glaucomatous eyes are excluded and also applies to persons with unilateral fibrillopathy as other authors have shown (Sobhy Bey 1932 Tarkkanen 19… Hansen & Sellevold 19 0)

Table II

Frequency of fibrillopathy at different levels of intraocular pressure

Intraocular pressure Schiotz 5 5 g	Total No eyes	With fibrillopathy	
		No eyes	per cent
0 0– 3 0	97	7	7 [illegible]
3 5– 4 0	300	17	5 7
4 5– 5 0	3136	28	0 9
5 5– 6 0	6315	28	0 4
6 5– 7 0	4986	23	0 [illegible]
7 5– 8 0	1833	3	[illegible]
8 5– 9 0	338	1	0 3
9 5–10 0	64	0	0
10 5–12 0	5	0	0
Total	17074	107	0 6

The frequency of open angle glaucoma can be seen from Table III The frequency among all persons with fibrillopathy was 22 7 per cent and was thus far higher than among persons without fibrillopathy (1 2 per cent) This difference has not occurred by chance (P < 0 001) The table also shows that an increase in the frequency of glaucoma with increasing age such as that found in persons

Table III

Frequency of open angle glaucoma among persons with and without fibrillopathy

Age (years)	With fibrillopathy			Without fibrillopathy		
	Total No persons	With glaucoma No persons	With glaucoma per cent	Total No persons	With glaucoma No persons	With glaucoma per cent
40–49	0	0	–	3091	16	0 5
50–59	10	3	30 0	2817	30	1 1
60–69	18	5	27 8	1811	36	2 0
70–79	23	4	17 4	453	9	2 0
80–89	23	5	21 7	269	11	4 1
90–99	1	0	–	21	0	–
Total	[illegible]	17	22 7	8462	10[illegible]	1 [illegible]

sequence of this will be that the follow up of persons with fibrillopathy but with normal intraocular aqueous dynamics need not be so rigorous as formerly assumed (cf Chandler 1959) If there are borderline findings on the first examination the chance that glaucoma will develop is considerably greater and such cases should be re examined at *regular intervals*

The factors mentioned above also indicate that there is undoubtedly *a causal relationship between fibrillopathy and increased intraocular pressure and thus between fibrillopathy and the development of glaucoma* If the co existence of the two conditions was due to chance one would expect for instance that in cases of unilateral fibrillopathy glaucoma would occur just as often in the fellow eye as in the eye with fibrillopathy

Summary

In the course of mass screening the intraocular pressure was found to average 17 5 mm Hg in 107 eyes with fibrillopathy and 14 5 mm Hg in 16 924 eyes without fibrillopathy

The whole of the distribution curve for intraocular pressure in eyes with fibrillopathy was displaced towards higher intraocular pressure compared with the curve in eyes without fibrillopathy

The frequency of glaucoma among persons with fibrillopathy was 22 7 per cent but showed no tendency to increase with increasing age The frequency was far higher than among per ons without fibrillopathy (1 2 per cent)

The increase in intraocular pressure appears to accompany or closely follow the development of fibrillopathy There is therefore relatively little danger of the later development of glaucoma in eyes with fibrillopathy and normal intra ocular aqueous dynamics

The results show *an undoubted causal relationship* between fibrillopathy and capsular glaucoma

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This tendency towards an increase in intraocular pressure has the result that *the whole distribution curve for eyes with fibrillopathy shows a shift in the direction of a higher intraocular pressure* than that shown in a corresponding curve for persons without fibrillopathy The curve for eyes with fibrillopathy like that for eyes without fibrillopathy, shows a relatively smooth transition from the normal range of intraocular pressure to pathological values Eyes with capsular glaucoma for instance are not marked by any particular elevated sector on the distribution curve It has been calculated that a reduction of the effective pore diameter by approximately 10 per cent is theoretically capable of explaining the displacement of the distribution curve for intraocular pressure observed in the present material in eyes with fibrillopathy (Davanger 1965)

As in most former materials the present study showed *a far higher frequency of open-angle glaucoma in persons with fibrillopathy than in persons without fibrillopathy* (cf Table III)

Unilateral cases of fibrillopathy associated with glaucoma are of special interest All the 8 such cases in the present study had glaucoma only in the eye with fibrillopathy Numerous other materials show comparable findings (Busacca 1928 Haemmerli 1928 Grzedzielski 1931, Sobhy Bey 1932 Horven E. 1935 Holst 1947 Weekers et al 1951 Wilson 1953 Gifford 1957 Stromberg 1962, Tarkkanen 1962 1965 Ogino et al 1963 Kristensen 1965)

The few cases in which glaucoma was demonstrated only in the eye without fibrillopathy (Trantas 1929 Wilson 1953) thus appear to be due purely to chance

The increase of intraocular pressure in eyes with fibrillopathy thus results in pathological pressure in 20–25 per cent of the cases A few cases fall in the borderline category but the majority do not develop glaucoma although a certain increase in pressure within the normal range may take place

Several factors indicate that the increase in pressure is closely associated in time with the development of fibrillopathy Firstly it was established that the average intraocular pressure in eyes with fibrillopathy in the present material did not increase with increasing age (Table I) Secondly the frequency of glaucoma in persons with fibrillopathy was if anything rather lower in older age groups than in younger (Table III) The follow up study showed that an increase in pressure accompanied or closely followed the demonstration of fibrillopathy in 6 of 14 initially unaffected eyes Finally it was found that only 1 of the 19 persons in whom fibrillopathy was associated with normal aqueous dynamics on mass screening had developed glaucoma 6–7 years later the remaining 18 showing unchanged pressures

It thus appears that the danger of the development of glaucoma in persons with fibrillopathy is on the whole present for a relatively short time after the development of fibrillopathy and then declines rapidly In practice the con

From the Department of Experimental Ophthalmology
University Eye Clinic Lund Sweden

ON REPEATED TONOMETRY

BY

C E T KRAKAU and K WILKE

The fact that repeated tonometry is associated with an apparent fall in intra ocular pressure was first noted by Stocker 1958 and Goldmann 1958 Since then it has been strongly confirmed (Moses 1961 Bechrakis 1966) and there is full agreement on the following points

1 When the measurements are repeated every minute there is a fall of 3 4 mm Hg in 5 minutes and about 5 mm Hg in 12 minutes According to Bechrakis the fall is exponential On the contralateral eye there is a sympathetic pressure fall

2 The decline in intraocular pressure is observed both on normal subjects and patients with glaucoma

3 The effect is found both on seated patients and on supine patients both with applanation tonometry and with Schiotz tonometers

On the other hand there are differences in opinion as to the effect of accom modation (Armaly Bechrakis) and anaesthetics

The mechanism of this phenomenon is still obscure and there are a few elementary questions to be answered before it can be tackled

1 Is the effect due to an interference from the measuring instrument or is the mere sitting at the instrument enough to elicit it? In the former case how soon is the presure restored?

2 Is the weight of the instrument resting on the cornea of any importance to the magnitude of the effect? Is it possible to measure the intraocular pressure at all without provoking the effect?

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A few series of experiments have been performed in order to answer these questions and make further studies of the phenomenon possible

Method

Local anaesthetics (Novesin 0 4 p c) were used in both eyes Tonometry was performed by means of the Goldmann applanation tonometer and a vibration tonometer (Krakau 1970) Distant fixation was used

The applanation tonometer rests on the cornea with a weight of 0 1 gm per mm Hg The vibration tonometer can be loaded with arbitrary weights in the present investigation 0 6 0 3 and 0 1 gm were used The vibration tonometer tested on an enucleated eye connected to an open manometer system shows slightly higher values the lighter the weight but no appreciable change in the slope scale reading/i o p

Results

1 On five seated patients six successive measurements were made every minute with the applanation tonometer Only the right eye was measured There was an appreciable fall of 4 6 (mean) mm Hg from an initial level of 18 6 mm Hg (mean) The same procedure was repeated on another day on the same patients though in this series they had been sitting in position for measurement at the instrument for ten minutes before any measuring was started Anaesthesia was given both before the patients were placed at the instrument and immediately before the measurements In this series there was a fall of 4 2 mm Hg (mean) from a starting level of 19 2 mm Hg (mean) (Fig 1) The pressure fall obviously does not start until measurements are made and the mere sitting is not enough to elicit the effect

The contralateral eye measured at the beginning and end in a number of cases showed a decrease of nearly the same size as the eye measured every minute Single measuremnts five minutes apart did not give a pressure decrease

The restoration of the intraocular pressure was studied in a group of 23 patients After the usual sequence of 6 measurements with applanation tonometer there was a mean fall in i o p of 4 mm Hg In a group of the patients measured after a further 5 min the pressure was restored to more than 50 per cent in another group measured after 15 minutes it was restored practically totally and in the last group measured after 20 min the pressure was 1 mm Hg higher than at the start of the experiment



Fig 1

Mean i o p of five patients Fulldrawn line patients seated in position for measurement at the applanation tonometer for 10 minutes before start of the measurements Dotted line measurements started without delay

2 On sixteen normal patients six consecutive measurements were made one minute apart The patients were seated and the same eye was measured throughout the entire experiment Four diffrent series were made one with the applanation tonometer and three with the vibration tonometer one for each of the loading weights 0 6 0 3 and 0 1 gm

The series were taken in random order and only one series per day The mean values of the four series are shown in Fig 2 The decrease from the initial to the 5 minute determination was 2 9 mm Hg for the applanation tonometer series and 1 5 1 1 and 0 4 mm Hg respectively for the vibration tonometer when 0 6 0 3 and 0 1 gm weights were used

The differences in pressure decrease between different combinations of series were tested by th t test The mean calculated from the sum of the pair differences (for instance = (Appl diff) − (Vibr diff 0.3)) was tested with the hypothesis mean = 0 Accordingly we find

	Pair difference	
Appl − $V_{0.3}$	1 8	$p \leq 0\ 001$
Appl − $V_{0.1}$	2 5	$p \leq 0\ 005$
Appl − $V_{0.6}$	1 4	$p \leq 0\ 10$
$V_{0.6}$ − $V_{0.1}$	1 1	$p \leq 0\ 10$

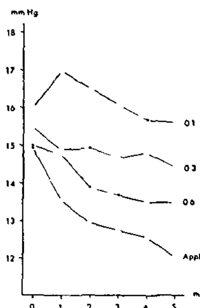


Fig 2
Mean i o p of 16 patients measured with applanation tonometer and vibration tonometer loaded with 0 6 0 3 and 0 1 gm

It is concluded that tonemetry influences the variable it should measure though to a slighter extent the lighter the instrument A local effect on the cornea is not likely since the contralateral eye is also affected

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*The Institute of Neurophysiology University of Copenhagen
and the Laboratory of Clinical Neurophysiology
Rigshospitalet Copenhagen*

THE NORMAL ELECTROMYOGRAM FROM THE EXTERNAL OCULAR MUSCLES

BY

SVEND FAURSCHOU JENSEN

Special problems are posed by recording the potentials of the motor units from the external ocular muscles because these muscles are flat and thin the motor units small and an ocular muscle relaxes only during maximum contraction of its antagonist

In previous studies the duration and shape of the motor unit potentials could not be assessed with certainty because the same action potential was not re produced wih sufficient accuracy This was due in part to an inconstant position of the electrode in relation to the fibres of the motor unit owing to the stiffness and weight of the electrode and in part to interference by activity from more remote units

The aims of the present study were therefore (1) to construct a light and flexible electrode and (2) to obtain a normal material and compare the param eters of the action potentials with the findings in skeletal muscles

Method

The concentric electrode was 18–20 mm in length and had an outer diameter of 0 3 mm The inner core was a 50 μ platinum wire with a leading off area of 0 015 mm (Fig 1) Low weight (60 mg) and good flexibility were obtained

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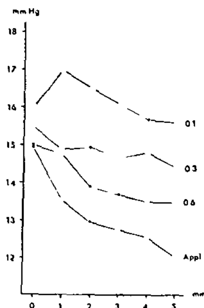


Fig 2
Mean i o p of 16 patients measured with applanation tonometer and vibration tonometer loaded with 0 6 0 3 and 0 1 gm

It is concluded that tonemetry influences the variable it should measure though to a slighter extent the lighter the instrument A local effect on the cornea is not likely since the contralateral eye is also affected

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of the same muscle potentials were recorded from at least 20 different units at 7–12 different positions of the electrode Thereby the mean duration of the potentials in each muscle was determined with an accuracy of 3 per cent and the mean amplitude of the potentials with an accuracy of 13 per cent

Statistical Analysis

The distribution of the duration and amplitude of the action potentials was characterized by the mean value and standard deviation The statistical significance of differences in duration and amplitude of the potentials was assessed by Student s *t* test (*Fisher 1946*)

Results

1 Influence of the Electrode Upon the Potentials

The influence of the cannula upon the shape, duration and amplitude of the action potentials was investigated by recording between the inner core and the cannula between the inner core and a remote electrode and between the cannula and the remote electrode (Fig 2) In the medial rectus muscle no potentials were recorded between the cannula and the remote electrode In a skeletal muscle the adductor pollicis action potentials recorded from the cannula and the remote electrode had a mean amplitude 30 per cent of the amplitude recorded from the inner core regardless of whether the cannula or a remote electrode was used as reference Therefore in the ocular muscles the cannula was truly indifferent

The distance between the leading off area of the electrode and the generator determines the amplitude of the potentials (Buchthal et al 1957 Ekstedt 1964) In the ocular muscles this was demonstrated by recording with a bifilar electrode When leading off between the cannula and one or the other inner core as well as between the two inner cores the bifilar electrode acts both as two concentric and as one bifilar electrode Since the leading off areas of the bifilar electrode are at right angles to the axis of the muscle fibres the distances usually differ between the two inner cores and the generator The mean amplitude recorded by the remote inner core was 37 per cent (115–73 μV) less than that recorded by the near inner core Since the distance between the two inner cores is 100 μ the reduction in amplitude is at least 400 μV per mm Since the mean amplitude of motor unit potentials in the rectus muscles is 100 μV this corresponds to a reduction in amplitude to one half over a distance of 0 13 mm and a reduction of 1/10 over a distance of 0 23 mm

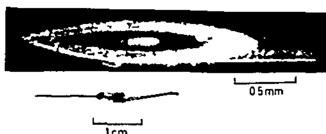


Fig 1
Leading off surface of the concentric electrode used for recording of potentials from the extrinsic eye muscles The area of the platinum core was 0 015 mm²

by *using a spiral (0 09 mm copper wire) to screen the two 50 mm long wires* (50 µ thick platinum wire) to the input of the amplifier The electrode could be sterilized by boiling

The leading off area of the electrode was about 5 times smaller than that used in electromyography of skeletal muscles the impedance and noise level were correspondingly higher When a current (AC) of 2–5 mA was passed for 20 sec through the electrode immersed in a 0 9 % NaCl solution the impedance was reduced from 200 kΩ to 30 kΩ measured at 500Hz

During recording from the ocular muscles the head end of the couch was elevated about 20° Five times at 2 min intervals a local anaestetic e g 0 4 % Novesine® Wander (oxibuprocaine chloride) was instilled into the eye The lids were kept apart with a blepharostat and the conjunctiva and muscle tendon were fixed by fine forceps The cornea was kept moist by instilling isotonic methyl cellulose 1 5 % The blepharostat was used for grounding

Recording was done with a 3-channel electromyograph (Disa 13 A 69) The input impedance of the amplifier was 100 MΩ parallel with 60 pF the noise level 2µV r m s The lower limiting frequency was 3 Hz the upper 10^4 Hz (3 db down)

Definition of Action Potential Parameters

The *interference pattern at maximum activity was characterized* by measurement of the amplitude of the envelope curve The duration of the motor unit potential was measured from the first deflection from the baseline to return to the baseline (total duration)

To reduce errors caused by interference from remote motor units the potentials were recorded during weak activity when only few motor units were functioning In addition each potential was recorded 3 times and the least distorted of the 3 potentials was measured To characterize the motor units

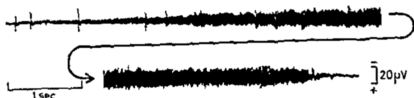


Fig 3

Increase in activity in the lateral rectus muscle when the eye was moved from full adduction (interference pattern) Note the potentials associated with the saccadic movements during transition from rest to full activity

30 per cent of the corresponding values for the biceps brachii and the mean amplitude 70 per cent (Fig 4) The standard deviations given in the histogram are based upon a considerably larger number of potentials than can be recorded in the individual patient and are therefore not applicable as a basis for assessing whether or not the duration of the potentials are abnormal Therefore the inter individual standard deviation of duration and amplitude was calculated as well In the ocular muscles the inter individual standard deviation was less than that in the biceps brachii whereas the standard deviation of the amplitude was only slightly below that in the biceps brachii (Table 1)

To decide with a 95 per cent probability whether a duration in a given muscle is abnormal the deviation from normal must be at least twice the inter individual standard deviation corresponding to ± 10 per cent in the ocular muscles and to ± 20 per cent in the biceps brachii (Sacco et al 1962) The corresponding differences for amplitude were ± 24 per cent in the ocular muscles and ± 33 per cent in the biceps brachii

Shape of Action Potentials (Fig 5)

In the ocular muscles in the biceps brachii 80–90 per cent of the recorded potentials were di or triphasic and 90 per cent of the potentials in the ocular muscles showed no irregularities In the biceps brachii only 50 per cent were regular In the recti muscles 3 4 per cent of the potentials were polyphasic (recorded from 10 muscles) as in the biceps brachii This means that the upper limit of normal in the individual patient (25 action potentials) is 12 per cent polyphasic potentials (Caruso & Buchthal 1965)

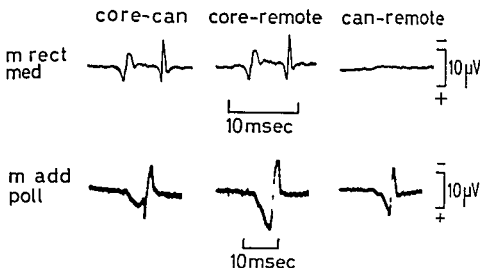


Fig 2

Pick up by the cannula of the concentric electrode in the medial rectus and the adductor pollicis muscle The remote electrode was a needle inserted in a fold of the conjunctiva (above) or subcutaneously at the wrist (below) The recording between the cannula (can) and the remote electrode showed that the cannula did not pick up a potential when recording from the medial rectus muscle but recorded a potential in the adductor pollicis muscle

Doubling the leading off area of the concentric electrode by short circuiting the two inner cores in the bifilar electrode caused a 6 per cent increase in the duration ($p < 0.05$) and a 16 per cent reduction in the amplitude of the potentials ($p < 0.01$)

2 Action Potential Parameters in Normal Subjects

The normal material comprises 20 muscles (10 lateral and 10 medial rectus muscles) from 15 persons ranging in age from 20 to 42 years (average 30 years) and 4 recti muscles from 4 persons aged 62–75 years None of the subjects showed signs of neuromuscular diseases In all cases recordings were also made from the biceps brachii by an electrode with a leading off area of 0 07 mm^2

Fig 3 shows an example of the increase in activity in a rectus muscle when passing from rest to activity The mean amplitude at maximum *contraction* in the recti muscles and in the biceps brachii is listed in Table I To be significantly reduced ($p<0.05$) an amplitude in a given ocular muscle must be 56 per cent below normal The corresponding difference for the biceps brachii is 28 per cent

The mean duration of the motor unit potentials in the ocular muscles is about

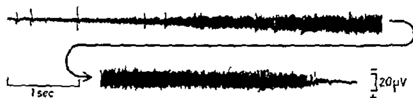


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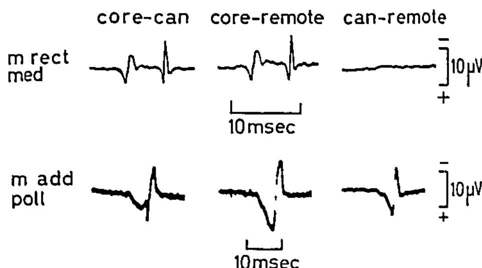


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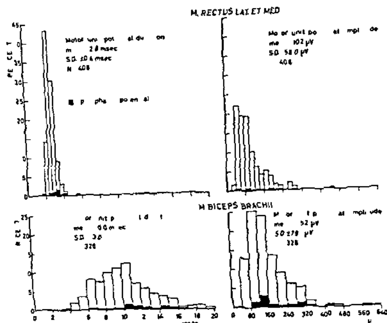


Fig. 4

Distribution of duration (left) and amplitude (right) of motor unit potentials in the lateral and medial rectus and the brachial biceps muscle. The black columns indicate polyphasic potentials (potentials with more than four phases). 15 normal subjects 20–42 years old.

Discussion

Since the resistance to movement of the light, flexible concentric electrode was slight, well defined and reproducible action potentials were recorded from the recti muscles during weak activity when the position of the electrode in relation to the activated units did not change.

It was demonstrated that the cannula of the concentric electrode was truly indifferent when recording from the eye muscles. There are presumably two explanations: (1) The *generators* are about 50 times smaller in the ocular than in the skeletal muscles and thus the field around each generator is smaller than in skeletal muscles. Therefore a *relatively large* leading off area, such as a cannula, picks up a small mean potential, since the potential is distributed over a large surface. The leading off area of the cannula *in situ in the ocular* muscles is about 0.5 mm, i.e. 50 times larger than that of the inner core. (2) The shunt of lacrimal fluid between the cannula and the remote electrode reduces the potential between these two electrodes. The correctness of these explanations

Table I

Mean duration mean amplitude of motor unit potentials amplitude of the pattern during full effort and inter individual variation in the ocular recti and brachial biceps muscles (15 normal subjects 20–42 years old)

	Mean duration msec	SD	SD %	Mean amplitude microvolt	SD microvolt	SD %	Amplitude during full effort microvolt	SD microvolt	SD %
m recti lat et med	2 8	0 1	4	102	12 0	12	359	101	28
m biceps brachii	10 0	1 2	12	152	25 0	16	2100	300	14

have been recorded from the laryngeal muscles by Fåborg Andersen (1957) In the cricothyroid muscle he found the end plates to be localized to the middle of the muscle in a narrow zone which made up 15 per cent of the muscle length

With respect to the age dependence of the potential duration (Sacco et al 1967) the ocular muscles behave like the small muscles of the hand There was no difference in duration between the age groups 20–40 and 60–70 years The duration of the motor unit potentials in the recti muscles found in the present study is 75–100 per cent longer than reported by Bjork & Kugelberg (1953) and others (Table II) The electrode used by Bjork & Kugelberg was presumably just as light and flexible as that used in the present study but interference from remote units is more marked when recording by unipolar than by concentric electrodes (Buchthal et al 1954) In the skeletal muscles the mean potential duration is the same whether the recording is with unipolar or concentric electrodes The potential durations found in the present study are longer than those found by Bjork & Kugelberg presumably because the initial and terminal parts of the potentials could more easily be distinguished In other studies of the duration of the potentials (Teasdall & Sears 1959 1960 1962 Gamstorp & Kupfer 1960) concentric electrodes were used which were heavier and less flexible than mine Therefore weak contractions could not be recorded and components of low amplitude were masked by interference from other units

Polyphasic potentials were not found by most previous authors (Bjork & Kugelberg 1953 Papst & Esslen 1961 Marg et al 1959 Breinin 1962) Teasdall & Sears (1960) found 2 per cent polyphasic potentials In the present material there were 3 4 per cent polyphasic potentials in recording from 20 muscles the same incidence as in most skeletal muscles and different from the muscles innervated by the facial nerve in which 6 per cent of the potentials are poly phasic (Buchthal & Rosenfalck 1955)

The standard deviation of the mean amplitude is larger and of the same magnitude in both muscles As demonstrated by experiments using the bifilar electrode in the ocular muscles small changes in the distance between the electrode and active muscle fibres may cause marked variation in the amplitude of the potentials

In comparing the maximum amplitudes in the recti muscles and in the biceps brachii it must be borne in mind that normally the contraction of the ocular muscles is not isometric But in cases where the eyeball has been immobilized (endocrine ophthalmoplegia and orbital fracture) I have recorded maximum amplitudes from the recti muscles not differing from normal As in the skeletal muscles it is possible to record 4–6 different action potentials in the recti muscles at one position of the electrode This indicates that within the area of *the motor unit* there are muscle fibres from other muscle units After correction of Torre's values from 1953 for small motor nerve fibres and for *sensory nerve* fibres (Buchthal 1961) there are about 13 muscle fibres in the motor unit of

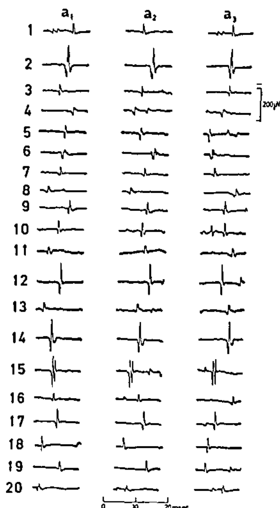


Fig 5
Three samples ((a_1 a a_3) of each of twenty different motor unit potentials from a normal rectus muscle

is indicated by the fact that even at maximum effort the potentials between the cannula and the remote electrode were only 25 μV as compared with 150 μV when recording between the inner core and the remote electrode The short duration of the motor unit potentials of ocular muscles reflects the small number of fibres belonging to each unit The standard deviation of the duration of action potentials in the recti muscles was less (14 per cent) than in the biceps brachii (28 per cent) The explanation is possibly that the motor units vary less in size in the ocular than in the skeletal muscles and that the motor end plates cover a smaller area than in the skeletal muscles This is also manifest in fewer potentials with irregularities in the ocular than in the skeletal muscles Action potentials of a similar short duration and with a similar standard deviation

the ocular muscles With a mean diameter of 15 μ these 13 muscle fibres laid beside each other would just be able to cover the leading off area of the electrode Moreover the electrode can pick up action potentials from other motor units adjacent to the margin of the leading off area

Summary

Motor unit potentials in the external eye muscles were recorded with a light and flexible concentric electrode The parameters of the motor unit potentials were determined for comparison with pathological conditions Corresponding to the smaller motor units the total duration was about 1/4 (2 8 msec SD 0 4 msec) of the duration in the biceps brachii muscle and the amplitude 2/3 (100 μV SD ± 58 μV) The total duration was 75–100 per cent longer than previously described because the initial and terminal components of the potentials could be discriminated With 20 different potentials from a certain muscle a mean duration of less than 2 5 msec and more than 3 1 msec is abnormal ($p < 0.05$) The normal limits of amplitude are 78 and 126 μV

The cannula of the electrode does not record action potentials in the eye muscles in m adductor pollicis the potentials recorded by the cannula have an amplitude 30 per cent of that recorded by the inner core

The amplitude of the potentials was reduced to one half at a distance of 0 1 mm and to 1/10 over a distance of maximally 0 2 mm

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Table II

Electromyography in the external eye muscle Previous findings and present study

	Motor unit potential from the rectus muscles							Amplitude during full effort microvolt	Electrode	Leading off area or diameter of electrode
	number potentials (1)	duration msec	SD	SE	amplitude microvolt	SD	SE			
Bjork & Kugelberg 1953	56 (8)	1 6	0 44	± 0 06	108	60 8	± 9 2		unipolar	0 001 mm²
Boudet et al 1961	–	1 0			*300–400*				bipolar	0 6 mm
Breinin 1955–57–62	–	1–2							concentric	
Burger & Kress 1959		1–2			20–200				concentric	0 25 mm
Davidson 1960		1–2			20–150					
Gamstorp & Kupfer 1960	2a (7)	1 7	0 2	± 0 06						
Huber & Lehner 1956		1–2							*concentric*	0 42 mm
Magora et al 1968	2b	0 9–1 5	0 06		20–1000			200–400	unipolar	0 040 mm²
Papst & Esslen 19		1–2			340–460	35 0				
Skorpil & Vladykova 1962		1–2			200–1000			200–400	concentric	0 42 mm
Teasdall & Sears 1959–60	50	0 5–2 0			50–150				*concentric*	
		1 43			358				concentric	0 1 mm (3)
Teasdall & Sears 1962	(10)	1 34	0 07							
Viallefont et al 1961		1–2							concentric	0 1 mm (3)
Own investigations	408 (15)	2 8	0 4	± 0 03	102	*58 8*	± 2 87	500 *359 ± 101*	*concentric*	*0 015 mm²*

1 In brackets number of subjects
2a 10 muscles
2b 60 muscles
3 Diameter of inner core

The Ophthalmic Pathology Laboratory (Head S Ry Andersen M D)
University Hospital Copenhagen
and the Department of Ophthalmology (Head V Clemmensen M D)
Central Hospital Næstved Denmark

PRIMARY MENINGIOMA OF THE ORBIT INVADING THE CHORIOID

Report of a case

BY

O BJÖRN HANNESSON

Primary meningiomas of the orbit are rare although meningiomas constitute 17 per cent of all tumours of the central nervous system According to Christensen & Ry Andersen (1952) meningiomas account for about 20 per cent of the tumours of the optic nerve Meningiomas are slowly growing tumours which are locally invasive but do not metastasize They appear most commonly at the age of 40–50 years and according to Reese (1963) orbital meningiomas are proportionatelly less rare in children than in adults Reese (1963) found 11 (5 per cent) meningiomas in a series of 230 consecutive cases of expanding lesions of the orbit with unilateral exophthalmus and in a histopathological study 28 meningiomas (3 per cent) were found in a series of 877 consecutive cases of such orbital lesions In a recent histopatholocical study Eldrup Jørgensen (1970) found 4 meningiomas (3 per cent) in a series of 150 primary orbital tumours On the other hand Forrest (1949) found as many as 17 meningiomas (9 per cent) in a series of 184 primary orbital tumours

Orbital meningiomas can originate within the cranial cavity in the optic canal or in the orbit but often the site or origin is impossible to establish Primary meningiomas arising within the orbit are rare compared with the secondary which invade the orbit from within the cranium (Reese 1963)

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Fig 1
X ray picture of the skull showing the expansive lesion in right orbit with destruction of the cheek bone.

was totally destroyed There was a small calcareous density in the middle of the orbital cavity There was no visible enlargement of the optic foramen

The patient was operated on by exenteration of the orbit The tumour was removed radically There were no postoperative complications The patient received an exoprosthesis and felt satisfied with the cosmetic result She was followed with clinical examinations for one year with no signs of recurrence. Five years after the operation she is subjectively well

The excised tissue measured 7 × 6 × 5 cm and contained the eyeball with the eyelids (Fig 2) The eye was phthisic with a thin cornea and detached retina On microscopic examination (Ophth Path Lab No 652/65) the tumour was found to be highly vascular and embedded in hyalinized connective tissue It was composed of moderate size cells with round to oval pale nuclei slightly polymorphous but with no mitoses The cells formed palisades and many whorls There were also transitions from whorls to psammoma bodies The tumour invaded the chorioid from the posterior pole of the eye up to the posterior part of the ciliary body (Fig 3 and 4) It was classified as a meningioma of the transitional type

The origin of the tumour could not be established Clearly however it

Walsh & Hoyt 1969) Craig & Gogela (1949) of the Mayo Clinic were able to collect only 17 meningiomas that were primary in the orbit although in a different series of 148 meningiomas located in the region of the anterior fossa of the cranium they found 35 that were invading the orbit most of them arising just outside the orbit at the sphenoidal ridge

The author has examined a total of 10 Danish cases of intraorbital meningiomas (8 primary and 2 secondary) in the files of the Ophthalmic Pathology Laboratory in Copenhagen The present case is the only one among them where an intraocular growth was demonstrated There seem to be only few reports of cases where the tumour extends intraocularly (Enoche Duval Hervouet & Lenoir 1955 Dunn & Walsh 1956 see Martin & Schofield 1957, Hogan & Zimmerman 1962) Thus the incidence of this growth pattern seems low which warrants the publication of the case

Case Report

(Dept of Ophth , Central Hospital Næstved Record nr 341/656)

The patient a widow aged 56 was injured at the age of 14 years by a straw in her right eye after which the vision of the eye permanently failed She was not medically examined at the time therefore the original extent of the injury is unknown Exophthalmus of the right eye was noted about 18 years later It gradually increased but had remained almost stationary during the 8 years before admission to the hospital There were no other CNS symptoms but she now asked for surgery for cosmetic reasons

On admission she was found to be in good general condition except for extreme adiposity and moderate hypertension Neurological examination was normal except for the ocular findings

The right eye showed a monstrous proptosis with the eyeball embedded in a big tumour which was firm lobulated and slightly painful on palpation The eyelids were markedly stretched and the conjunctiva was moderately injected Ocular movements were restricted with very little horizontal mobility remaining The pupil was dilated and fixed and the eye was amaurotic The cornea was enlarged but clear and the iris was atrophic There was an aqueous flare The lens was cataractous and subluxated backwards prohibiting examination of structures behind it

The left eye was normal

Erythrocyte sedimentation rate was slightly increased other routine chemical laboratory tests were normal Chest X ray showed no appreciable disease Skull X ray tomography (Fig 1) the right orbital cavity was much enlarged the roof and the medial orbital wall were very thin and the right cheek bone

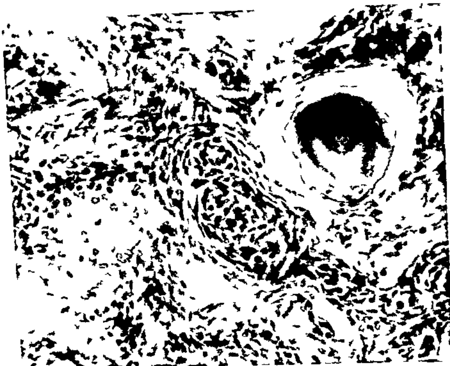


Fig 4
Whorls and psammoma in the extraocular part of the tumour × 410

was primary within the orbit as the optic foramen was not visibly enlarged despite the very long duration of the disease leading to severe destruction of other parts of the bony orbit.

Trauma (including foreign bodies) has frequently been suggested as a cause of tumours also meningiomas (Cushing & Eisenhardt 1938 see Turner & Laird 1966 Schultze & Bingas 1968) Actually foreign material has in some cases been found in the centre of the tumour In the present case there is a history of a trauma by a foreign body with ensuing deteriorated vision which could fit with a traumatic aetiology but proofs of this are lacking

Summary

A case of monstrous primary orbital meningioma of at least 24 years duration is presented The tumour invaded the chorioid up to the posterior part of the ciliary body this is very rare

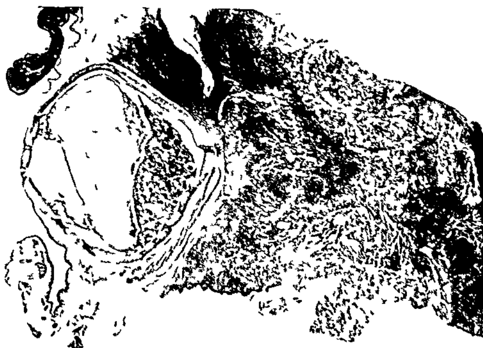


Fig 2
Survey micrograph of the excised eye and tumour The tumour can be seen to extend intraocularly in the posterior pole of the eye × 2 6

Fig 3
Intraocular part of the tumour at the sclera There are numerous vessels and psammoma bodies × 65

From The Department of Experimental Ophthalmology
University Eye Clinic Lund Sweden

VISUAL ACUITY WITH BRIEF STIMULI

BY

GÖRAN STIGMAR

Key words vernier acuity stereo acuity resolving power short exposure

Abstract

Vernier acuity stereoscopic acuity and resolving power (resolution) have been determined for eight different exposure times ranging from 4 sec to 0 025 sec, at two levels of luminance with a technique which permits examination under identical conditions for the three visual functions The results of this study can be summarized as follows

1 If the exposure time is longer than 0 8 sec a four fold decrease of the luminance of the retinal image influences the three kinds of acuity differently Vernier and stereoscopic acuities seem to be independent of a reduction of luminance within this restricted range contrary to the resolution thresholds which are *significantly increased* For exposure times shorter than 0 8 sec however also vernier and stereoscopic thresholds are increased by a reduction of the luminance level

2 For resolution there is a reciprocal relationship between intensity and time according to the formula $I \times t = \text{Constant}$ when the exposure time is 0 8 sec or shorter This relation between intensity and time could not be shown for vernier and stereoscopic acuities

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of the eye as well They found a t_c value of about 0 5 sec, and below exposures = 0 1 sec they could demonstrate a strict reciprocal relationship between intensity and time (I × t = C) for all levels of acuity At constant intensity the same authors found that acuity increased with the logarithm of the exposure time in a sigmoid manner

In other experiments however a critical duration of about 0 1 sec was found to be valid only at moderate levels of intensity In fact the critical duration varies between 0 01 sec and 1 0 sec at high and low intensities respectively (Jaeger 1952 Martin et al 1950)

There are only a few investigations concerning the dependence of *vernier acuity* on illumination and exposure time In one of them Baker (1949) studied the acuity intensity relation but only at two different lengths of exposure times She found an impairment of the visual responses for short exposures (0 019 sec) compared with long exposures but the maximum acuity for short exposures even at high intensities was never as high as that obtained with long exposures The simple reciprocal relation between time and intensity found by Graham & Cook (1937) for resolving power could therefore not be verified for vernier acuity This can also be concluded from the results of an earlier investigation by Averill & Weymouth (1925) who had studied the vernier function for two different length of exposures (0 03 and 1 5 sec)

Of special interest for this investigation have been the results of Keesey (1960) who studied three visual functions – vernier acuity fine line acuity and resolving power with grating – for varying exposure times Even if the experiments by Keesey were not performed to make a comparison between different visual tasks under conditions of short exposures but for studying the effect of the involuntary eye movements (micro nystagmus) on visual acuity the results can also be evaluated for our purpose If only vernier and resolving power are considered no clear difference between the threshold variation of the visual functions can be seen with exposure times ranging between 1 28 to 0 02 sec. The critical duration (t) is also about the same (0 2 sec) for the two visual functions

The extent to which duration of the test stimulus affects *stereoscopic acuity* seems to be a problem more intriguing than that of the other two kinds of vision

Ogle & Weil (1958) have made an extensive review of earlier investigations in this field They came to the conclusion that the results previously obtained did not support a definitive relationship between exposure times and stereoscopic acuity In their own experiments however they could demonstrate a strong correlation between acuity and time. If their data were plotted on a log log coordinate system the relationship could be described by a straight line. The decrease of exposure times from 1 0 to 0 006 sec resulted in a four fold increase of the thresholds.

3 Decreasing exposure time influences stereoscopic acuity more than vernier acuity and resolution There exists a simple approximately quadratic relationship between vernier and stereoscopic thresholds which can be expressed by a straight line if the two acuities are plotted against each other in a log log scale. The same relationship is found for both levels of luminance

4 Stereoscopic acuity is deteriorated more than vernier acuity if a low degree of heterophoria is introduced under conditions of short exposure times. This is in contrast to performances with long exposure times where neither of the acuities were influenced by an induced heterophoria

Introduction

In previous investigations three types of visual functions – vernier acuity stereo acuity and resolving power of the eye – have been studied with a method which permits a continuous recording of the visual performances (Krakau 1967 Krakau & Stigmar 1971b Stigmar 1970 Stigmar 1971) Working with such a system where the observer is presented the visual task as a series of successive views for a period of time the duration of the test stimulus has to be taken into account

With an exposure time of up to 4 sec our trained observers could maintain their visual performances at a steady level for a considerable period of time for simple test patterns more than 15 min without getting tired In connection with such experiments the problem arose as to what extent visual acuity in a broad sense is affected if the observers are forced to make their interpretations within a shorter exposure time

A number of experiments have been performed for various purposes under conditions of short exposure times Only a few of them will be referred to here since extensive expositions are available elsewhere (Bartlett 1966 Riggs 1966)

It has been known for a long time that all visual performances are dependent on the exposure time if the duration of the stimulus is below a certain critical value (t_c) For exposure times longer than this critical duration visual discrimination occurs independently of time or with only minor variations

In most earlier investigations with brief stimuli the acuity was studied for different kinds of visual tasks as a function of duration and intensity of the stimulus A simple reciprocal relation between these two variables was first found to exist in determinations of absolute thresholds of light sense but later Graham & Cook (1937) demonstrated a similar relation for the *resolving power*

In the vernier situation the test object consisted of a three line test with the test details horizontally orientated when produced on an oscilloscope screen The Dove prisms were adjusted in order to give a vertical orientation of the test image of the object with the vernier offset either to the right or to the left (Test object type (A/) in the paper by Stigmar *1971*)

The same type of test object was also used for the stereo situation The trans verse *disparity necessary for the stereo perception* was accomplished by turning the image for one eye 180 degrees from its vernier position which corresponds to a rotation of one of the Dove prisms 90 degrees on its axes

The resolving power was determined with a target described by Krakau & Stigmar (1971b) It consists of two parallel lines each of them subtending an angular length = 20 min arc These lines were also imaged as vertically orien tated when observed through the Dove prisms For each kind of visual situation the examination was performed by presenting to the observer the test object in one of the following two alternatives right or left (vernier) in front of or be hind (stereo) two lines or one broad band (resolution) The degree of diffi culty of the test object was automatically adjusted by the observer s skilfulness

Since the test objects were generated on an oscilloscope a series of well de fined *exposure times was easily accomplished by electronic means* Eight ex posure times were used 4 0 2 0 0 8 0 4 0 2 0 1 0 05 0 025 sec

For the two longest exposure times the subject had to make his choice within 4 sec and 2 sec respectively For the other exposure times the short presentation of the object was followed by a pause The length of the pause and exposure time together was always 4 sec If no interpretation was made within the times mentioned it was ranked as a wrong one and was subsequently followed by a target easier to discriminate

The three types of visual acuity were examined for the various exposure times at two levels of luminosity of the test object In series 1 the maximum lu minance of the oscilloscope lines was about 100 cd/m² at the peak of maximum luminance (Krakau & Stigmar 1971a) In series 2 the luminance of the retinal images was reduced by neutral *gray filters with a transmittance of 25 per cent* The filters were inserted in front of the prismatic device one in front of each eye

By making small corrections of the positions *of the Dove prisms in the fronto* parallel plane any type of heterophoria could be corrected. In this way the testing *procedure could* be performed with the eyes in an orthophoric position (in series 1 and 2) a fact which is essential particularly when short stimuli are used in the stereo discriminative situation

In another series series 3 a slight degree of heterophoria was induced by placing two ° diopter prisms base in in front of each eye Only vernier and

Ogle & Weil suggested that their results were best explained by the influence of the normal physiological ocular nystagmoid movements of the eyes (cf Ogle 1962)

In an investigation with stabilized image technique, Shortess & Krauskopf (1961) studied the influence of short exposure times but they failed to show any significant difference of performance if compared with results obtained under normal viewing conditions Their conclusions are in agreement with those drawn by Keesey (1960) for vernier acuity

If the data obtained by Shortess & Krauskopf (1961) are compared with those of Ogle & Weil (1958) we will find essentially the same time acuity relationship in these two investigations Their observations suggest that stereoscopic acuity is influenced by the exposure time to a greater extent than the other two kinds of acuities considered in this study

A time dependent difference between vernier and stereoscopic acuity has also been described by Richards (1951) in a study on the effect of alternating views of the test object He found that vernier discrimination was possible at an alternation rate of 20 cycles/sec compared with only 4 cycles/sec in a stereoscopic discriminative situation

Although a great number of experiments have been performed with brief stimuli for varying purposes only few of them were so designed that they permit a comparison between different kinds of visual functions From these earlier observations it is still not clear whether any basic differences exist between various kinds of visual acuity when they are examined under identical conditions *The present investigation is an attempt to obtain an answer to this question* as regards three types of visual functions vernier stereo and resolving power (resolution)

Method

The experimental procedure and the automatic technique for testing the three types of acuity have been extensively discussed in previous papers (Vernier and stereo acuities Krakau 1967 Stigmar 1970 1971 resolution Krakau & Stigmar 1971b) It is sufficient therefore to mention only some essential and additional details

The test objects were composed of luminous lines on an almost dark background The peripheral visual field was slightly illuminated in order to make the fusional stimuli stronger Irrespective of the type of vision tested the test object was observed binocularly through a pair of Dove prisms

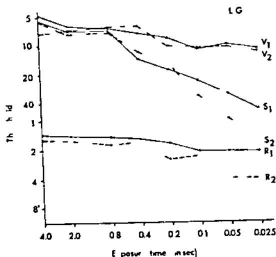


Fig 2
Acuity curves for subject L. G Symbols the same as in Fig 1

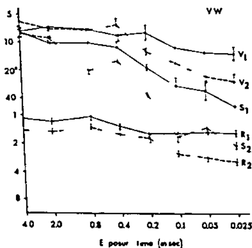


Fig 3
Acuity curves for subject V W The vertical lines indicate the standard deviations. Symbols the same as in Fig 1

stereo acuities were examined but in other respects the experimental arrangements were identical with those in series 1

Three experienced subjects took part in the experiments in series 1 and 2 two subjects in series 3 The subjects had normal corrected visual acuities at Monoyer s letter charts Their refractions ranged between + 0 5 and − 0 5

For each kind of visual situation the individual judgements were recorded as a step curve The examination time was 3 5 min but only the last 2 5 min was used for the calculation of the threshold value (schematic illustrations of the curves and details on the statistical treatment are available in papers by Stigmar (1970 1971) and Krakau (1967)

Results

Series 1 and 2

The data obtained with objects of high luminance (series 1) and reduced luminance (series 2) are presented in the accompanying table The results are also graphically illustrated in Figs 1–3 which show log visual thresholds as a function of log exposure time The threshold values are the mean values of the level

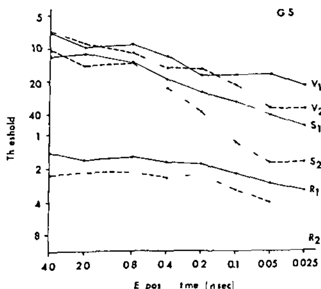


Fig 1

Vernier acuity (V) stereoscopic acuity (S) and resolution (R) as functions of exposure time at two levels of luminance (Series 1 and 2) Subject G S

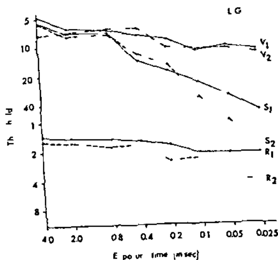


Fig 2
Acuity curves for subject L. G Symbols the same as in Fig 1

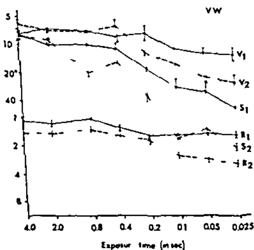


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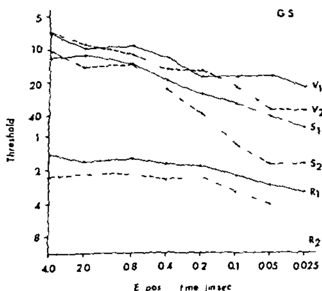


Fig 1

Vernier acuity (V) stereoscopic acuity (S) and resolution (R) as functions of exposure *time at two levels of luminance (Series 1 and 2) Subject G S*

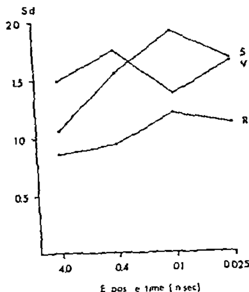


Fig 4
The average standard deviations for three subjects as a function of exposure time.

by the duration of the stimulus provided that the exposure times are shorter than ?–0 ? sec Since there is a gradually increasing slope of the acuity curves within this range it is impossible to define a certain critical exposure time (t_c) beyond which the acuity is not influenced by the duration of the stimulus There are some individual variations of the slope of the curves but it is evident that stereo acuity is more influenced by short exposure times than the other two kinds of vision

Series 3

In this series a low degree of heterophoria was introduced by placing two 2 diopter prisms base in in front of each eye Vernier and stereo acuities were examined and recorded as in series 1 For the two subjects investigated the results were essentially the same and for one of them (G S) the data obtained are presented in Fig 5 In order to make a comparison easier the performances obtained in series 1 (V_1 and S_1) are also indicated in this graph

Inspection of the curves shows that vernier and stereo thresholds over a greater part of the range of exposure times are higher than those obtained in

Table I

Vernier (V) Stereo (S) and Resolution (R) thresholds for eight exposure times V and S in seconds R in minutes of arc

Exposure time (sec)		4 0			2 0			0 8			0 4		
		V	S	R	V	S	R	V	S	R	V	S	R
Subject													
G S	S_1	7	12	1 5	10	11	1 7	9	14	1 6	12	19	1 8
	S_2	7	10	2 3	9	14	2 2	11	14	2 2	15	23	2 4
V W	S_1	8	8	1 1	7	10	1 2	[illegible]	10	1 0	9	11	1 3
	S_2	6	8	1 5	7	9	1 5	7	20	1 4	[illegible]	16	1 6
L G	S_1	5	6	1 4	6	7	1 5	7	7	1 5	8	14	1 6
	S_2	8	6	1 6	7	8	1 7	6	7	1 8	6	12	1 7
Exposure time (sec)		0 2			0 1			0 05			0 025		
G S	S_1	18	25	1 9	18	31	2 2	18	41	2 7	22	51	3 2
	S_2	15	39	2 3	22	74	3 1	36	111	4 1	36	109	8 6
V W	S_1	8	19	1 6	12	30	1 6	13	34	1 6	14	50	1 6
	S_2	13	38	1 9	17	107	2 6	24	86	2 9	27	133	3 2
L G	S_1	9	19	1 8	11	24	2 1	10	34	2 1	11	48	2 1
	S_2	11	16	2 5	11	35	2 4	11	61	4 1	13	107	4 1

of performance during the period (2 5 min) They correspond to a probability of seeing = 0 6 and they are calculated in terms of visual angles at the nodal point of the eye expressed in seconds (vernier and stereo acuities) or minutes of arc (resolution)

The dispersion of judgements in terms of standard deviation for each kind of visual performance has been calculated and found to be about the same for the three observers For one of them (V W) the standard deviation has been indicated on the curves as vertical lines In general it may be noted the standard deviation is lowest for resolving power if expressed in log units This can also be seen from Fig 4 where the average standard deviations for the three visual situations have been plotted against exposure time

Most of the individual curves show that the visual thresholds are influenced

one of the two buttons we have observed that most subjects prefer an exposure time of about 2 sec when they are familiar with the examination procedure.

Consequently in the present investigation we do not find any signs of impairment of the acuities in the range 4–2 sec The lower limit of the optimal performance also shows an inter individual variation For vernier acuity and resolution the subjects can maintain a high acuity level even when they are forced to make their decision within 0 2 sec or less Stereoscopic acuity however appears to require a longer exposure time ($\lesssim$ 0 8 sec)

Reduction of the luminance of the object influences the visual acuities differently (Figs 1 3) Thus in the whole range of exposures the thresholds of resolution are increased On the other hand vernier and stereoscopic thresholds are influenced only slightly or not at all by reduced luminance at exposure times higher than 0 4 0 8 sec

The data obtained are not in accordance with those of Ogle & Weil (1958) who conclude that for a given level of luminance of the adapting background the stereoscopic acuity is independent of the luminance of the objects seen in the depth This conclusion was partly based on their experiments with a flash light and with an *exposure time of 1/5000 sec and they probably hold only if one works with higher levels of energy According to the present findings vernier and stereo acuities are independent of a four fold decrease of luminance only if the exposures are about 0 8 sec or longer*

As mentioned in the introduction Graham & Cook (1937) have demonstrated a reciprocity between intensity of the stimulus and exposure time ($I \times t = C$) This simple relation did not hold for vernier acuity (Baker 1949) or for stereo acuity (Ogle & Weil 1958) From this point of view the average results for exposures $\lesssim$ 0 8 sec have been arranged in 4 energy levels as the product $I \times t$ plotted on the abscissa against the acuity levels on the ordinata (Fig 6)

The four pairs of products ($I \times t$) have been calculated in the following way

Between the retinal images without filter (I_1) and with filter (I) there is an intensity relation = 4 1 The exposure times have been arranged in pairs with the relation 1 4 according to the following table

Time	0 2	0 1	0 05	0 025	(I_1)
	0 8	0 4	0 2	0 1	(I)
	C_8	C_4	C	C_1	

Thus eight products $I \times t = C$ can be formed

$$C_8 = 0\ 8 \times I \approx 0\ 2 \times I_1$$
$$C_4 = 0\ 4 \times I \approx 0\ 1 \times I_1$$
$$C_2 = 0\ 2 \times I \approx 0\ 05 \times I_1$$
$$C_1 = 0\ 1 \times I \approx 0\ 025 \times I_1$$

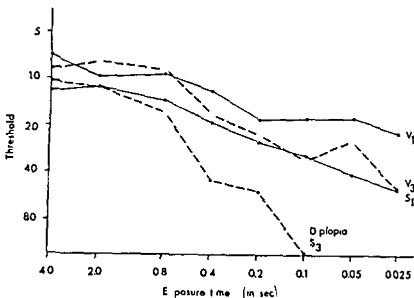


Fig 5
Example of vernier and stereoscopic performances for subject (G S) under orthophoric (Series 1) and heterophoric conditions (Series 3) respectively

the orthophoric state of vision It is also evident that stereo acuity is more affected than vernier acuity under this heterophoric state of vision providing the duration of the stimuli is short enough

Discussion

In some earlier series of experiments with continuous recording of vernier acuity stereo acuity and resolution the duration was limited to 4 sec since it was found that visual acuity did not improve beyond that time Moreover beyond a certain upper limit of exposure time the acuity may deteriorate For vernier acuity this has been shown by Foley Fisher (1968) and for stereoscopic acuity by Sachsenweger (1961) This upper limit of the range of optimal performance is probably imposed by the attention span of the observer (Ogle & Weil 1958) and this limit may vary interindividually (Foley Fisher 1968)

Our experiences are in accordance with these conclusions and in previous studies with our examination technique where the subject interrupts the visual display within a 4 second period as soon as he has made his decision by pushing

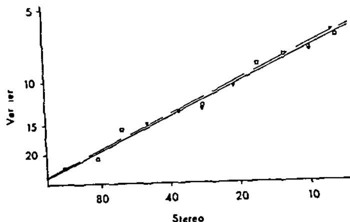


Fig 7

Scatter plot of the relation between vernier and stereoscopic thresholds for eight expo sure times ranging from 4 sec to 0 025 sec The triangles indicate the average threshold values for three subjects at the higher level of luminance the squares indicate the threshold values at the lower level of luminance The two regression lines represent the relations at the two levels of luminance Correlation coefficients for both series are 0 99

We find that this relationship is well approximated by a straight line of the slope 0 48 when a log log scale is used

This relation between vernier and stereoscopic acuities is equivalent to

$\frac{\eta}{\eta_i} = \left(\frac{\zeta}{\zeta}\right)^k$ where η is the stereoscopic and ζ_0 is the nernier threshold value at optimal viewing conditions and η and ζ_i the threshold values for dif ficult viewing conditions The constant k is about 2 This simple relationship also holds at the lower level of luminance the points still lie along the same line though in an extended range

The present limited material does not permit any far reaching conclusions but information theoretical speculations on a connection between vernier and stereo acuities may be tempting if the quadratic relation above can be con firmed

Vernier acuity and resolution are plotted against each other in a similar way in Fig 8 No similar simple relation seems to exist between these functions

Series 3 can be considered as a complement to an earlier study (Stigmar 19›0) where the importance of induced heterophoria for vernier and stereo acuity was investigated without restrictions of exposure time The results in that study indicated that a low or moderate degree of heterophoria does not influence the

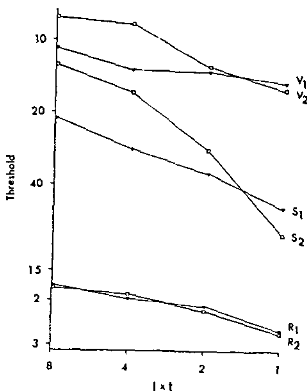


Fig 6

Vernier acuity stereoscopic acuity and resolution for four energy levels (I × t) The products I × t are expressed *in arbitrary units Further explanations in text*

For each kind of acuity and for each level of energy (C_8) we thus have two threshold values and if the visual performance only depends on the energy these two threshold values should be the same

As regards the data obtained in the resolution situation it is evident that our results fit the relation $I \times t = C$ in a satisfactory manner contrary to the data obtained in vernier and stereo situations These results are therefore consistent with the earlier findings mentioned

However the main purpose of the present study has been to investigate the relations between the acuities under conditions of short exposures The most striking feature of the individual curves in Figs 1–3 is the steep slope of the stereo curves for exposures in the range 0 4–0 025 sec indicating that stereoscopic acuity is more influenced by short durations of stimuli than the other two kinds of vision This fact is clearly illustrated in Fig 7 where vernier acuity has been plotted against stereoscopic acuity for corresponding exposure times

Acknowledgments

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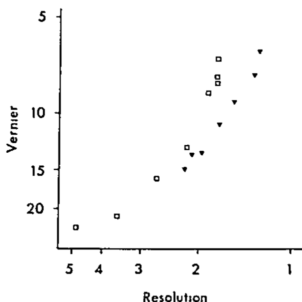


Fig 8
Scatter plot of the relationship between vernier acuity and resolution at two levels of luminance The symbols are the same as in Fig *7*

acuity levels From the present series however it is clear that the stereoscopic thresholds in particular are affected by an occulomotor imbalance when the stimuli are short enough These results are in direct accordance with those obtained in a clinical investigation by Sachsenweger (1956) who has emphasized that even fairly low degree heterophorias may decrease the stereo acuity under unfavourable fusional conditions

Now the question arises whether these findings may explain the steeper slopes of the stereo curves in series 1 and 2 also when the subjects were made orthophoric A definitive answer cannot be given but one has to recognize that during the intervals between short stimuli there are no central fusional stimuli which maintain the eyes in a strict orthophoric position Therefore a refixation from a small angle may be necessary in order to secure fusion of the central reference lines in the stereo situation

On the other hand for the vernier situation an optimal result can be achieved without fusion whereas monocular acuity with the best eye is as high as binocular acuity (Stigmar 1970) This may explain why stereoscopic acuity is affected more than the other two kinds of vision also in an orthophoric state of vision as it appears in series 1 and 2

The Otolaryngological Hospital University of Helsinki
(Head Prof U Siirala M D)
and the Helsinki University Eye Hospital
(Head Prof Salme Vannas M D)
Helsinki

OTORHINOLARYNGOLOGICAL PATHOLOGY IN PATIENTS WITH OPTIC NEURITIS

BY

JORMA TARKKANEN & AHTI TARKKANEN

The relationship of chronic sinusitis to optic neuritis has been exhaustively reviewed in the literature (Walsh & Hoyt 1969) This question became popular especially after a close anatomical relationship between the posterior nasal accessory sinuses and the optic nerve had been demonstrated (Shaeffer 1920) Great individual variations were observed but it was shown that one sphenoid sinus may come in contact with the optic nerve of the same side with the contra lateral optic nerve with the chiasm or with both nerves and the chiasm Various possible mechanisms by which paranasal sinus pathology could produce optic neuritis have been outlined Direct extension of infection to contiguous structures as well as toxic factors have been suggested Furthermore direct pres sure edema of the optic canal venous congestion and the resultant hypoxia have been considered (Campbell 1963) After all however firm opinion has been expressed that in most instances the apparent association between sinusitis and optic neuritis is fortuitous (Walsh & Hoyt 1969)

At the Helsinki University Eye Hospital a search for possible foci is being

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Author s address

Göran Stigmar Med lic,
The Department of Experimental Ophthalmology University Eye Clinic
Lund Sweden
Address for communications as above mentioned

Results

Incidence of sinus X ray abnormalities

In a careful review abnormalities of the X ray were *found in 12 out of* the 104 cases (11 per cent) The abnormalities found have been listed in Table I Purulent maxillary sinusitis was observed in 3 cases thickened mucous membrane in the maxillary sinus *in 3 cases and maxillary* sinus cyst in 3 cases In only 1 case were inflammatory changes present in ethmoid cells and in none of the cases were pathological changes found in the sphenoid sinuses

Results of follow up examination

X ray abnormalities were still present in 5 cases varying from thickened mucous membrane of the maxillary sinus to exceptionally large ethmoid cells In two of these *there were abnormalities of* the nasal smears and bacteriological cultures (Cases 6 and 10)

Concordance of the otolaryngological and optic nerve lesions

Table I *reveals that the right optic nerve was involved in 4 cases* the left in 7 cases and in one case both optic nerves were involved The otolaryngological lesion was ipsilateral in 7 cases and bilateral in 4 cases Hence in only one case was the otoloryngological lesion contralateral to the optic nerve affection and discordance was thus observed in 1 out of the 12 cases

Otolaryngological signs at the time of optic neuritis

In a retrospective review of the *charts and in repeated* questioning of the patients during the follow up examination it was found that 6 of 12 patients had experienced otolaryngological signs at the time of the appearance of the optic neuritis In 5 cases acute allergic or chronic rhinitis was present, and in 1 case the patient exhibited acute ethmoiditis and chronic tonsillitis (Table I)

Probable etiology of optic neuritis

In this study no attempt was made to determine the etiology of optic neuritis in each case However the suggested etiologies in the charts have been listed in Table I In only 1 case (Case 3) was *infectious etiology* due to maxillary sinusitis considered This patient had acute rhinitis and acute left maxillary sinusitis at *the time* of the appearance of the left optic neuritis In 4 cases no etiology was suggested and in 6 cases neurological examination had disclosed evidence of multiple sclerosis It is of special interest that in 5 of these definite

routinely carried out on patients with optic neuritis. All patients are subjected to sinus, teeth and chest X-ray examination, and those with positive radiological findings of the paranasal sinuses are referred to the Otolaryngological Hospital, University of Helsinki, for further studies. In the present study it was attempted to determine the incidence of positive radiological findings in a series of 104 consecutive patients with optic neuritis and to study the possible relationship of the otolaryngological and ocular conditions by a careful follow-up examination.

Material and Methods

Records of 104 consecutive patients with optic neuritis were reviewed. In this study optic neuritis was employed as a general term indicating involvement of the optic nerve as the result of any inflammation, demyelinization or degeneration (Walsh & Hoyt 1969). The age and sex distribution of the patients is seen in Fig. 1. There were 39 males and 65 females. The youngest patient was 17 years and the oldest 64 years old. 86 per cent of the patients were 49 years or younger. The sinus X-rays were reviewed again, and those patients with abnormal findings were subjected to follow-up examination consisting of repeated X-rays and thorough otorhinological examination. Nasal smears and bacteriological cultures from both nasal cavities were also obtained.

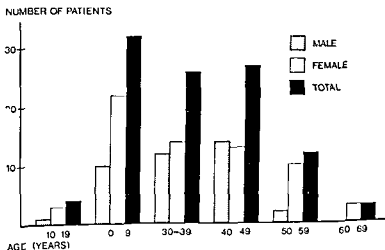


Fig. 1

Patients with optic neuritis classified by age and sex. 104 cases.

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Table 1
The patients with optic neuritis (O N) subjected to otolaryngological follow up examination

No of patient	Sex	Age	Side of O N	ENT at the time of O N	X ray finding at the time of O N
1	Female	40	Right	Acute rhinitis	Large ethmoid cell posteriorly adjacent to the right orbit
2	Female	30	Left	None	Large ethmoid cell lining a part of the medial wall of both orbits
3	Female	43	Left	Acute rhinitis	Left acute purulent maxillary sinusitis
4	Male	38	Right	Acute ethmoiditis Chronic tonsilitis	A large ethmoid cell with diminished air content and thick walls posteriorly adjacent t othe right orbit
5	Female	29	Left		Cyst in left maxillary sinus
6	Female	22	Left	Allergic rhinitis	Cyst in left maxillary sinus
7	Male	37	Bilat.	Chronic rhinitis Acute infection	Right purulent maxil lary sinusitis
8	Male	42	Right	None	Left purulent maxil lary sinusitis
9	Female	28	Left	None	Thickened mucous membrane in the left maxillary sinus
10	Male	36	Left	None	Thickened mucous membrane in both maxillary sinuses
11	Male	33	Right	Chronic rhinitis	Cysts in both maxil lary sinuses
12	Male	23	Left	None	Thickened lateral wall of the left maxillary sinus

MS = Multiple Sclerosis

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The patients with optic neuritis (O N) subjected to otolaryngological follow up examination.

X ray finding at follow up	Nasal smear at follow up	Bacteriological culture at follow up	Suggested etiology of O N
Large ethmoid cell posteriorly in the right orbit	Normal	Proteus vulgaris	MS
Large ethmoid cell lining a part of the *medial* wall of both orbits	Normal	Normal	Unknown
Normal	Normal	Normal	Infections due to maxillary sinusitis
Normal	Normal	Normal	MS
Thickened mucous membrane in the left maxillary sinus	Normal	Normal	
Normal	Eosinophils — Neutrophils + Goblet cells +	Staph aureus (resistant strain)	Unknown
Sclerotic lateral wall of the right maxillary sinum (Caldwell Luc operation)	Normal	Normal	MS
Normal	Normal	Normal	Unknown
Thickened mucous membrane of the left maxillary sinus	Normal Slight metaplasia	Normal	MS
Normal	Eosinophils ± Neutrophils ++ Goblet cells +	Pneumococcus	MS
Normal	Normal	Normal	MS
Not traced			Unknown

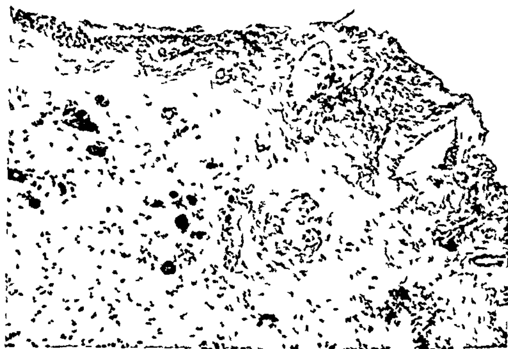


Fig 2

Chronic inflammation in the mucosa of the maxillary sinus in case No 7 Note atrophy of the mucosa and deformity in the few remaining glands ulceration of the surface and increased fibrous tissue (Giemsa stain × 300)

inflammatory changes were observed at the time of optic neuritis As an example the intensive inflammatory changes of the mucous membrane of the maxillary sinus of case 7 are shown in Figs 2 and 3 This patient had bilateral optic neuritis following acute febrile infection and chronic sinusitis Caldwell Luc operations had to be performed for the cure of the infection The vision never recovered however and neurological examination disclosed multiple sclerosis

Discussion

In our material X ray abnormalities of the paranasal sinuses were observed in 11 per cent In a study carried out at the Massachusetts Eye and Ear Infirmary 4 patients had demonstrable sinusitis out of the 38 cases with retrobulbar neuritis giving an incidence of 10 per cent To find the expected incidence of foci of infection in presumably otherwise normal persons 507 patients with cataracts



Fig 3

Chronic maxillary sinusitis in case No 7 Dense, nonspecific inflammatory is illustrated as well as the total abscence of glandular elements of the atrophied mucosa (Giemsa stain × 300)

ocular trauma and other ocular pathology were studied for foci and positive findings were obtained in 13 per cent (Guyton & Woods 1941)

In a routine search for foci one may be prepared to obtain negative findings in about 90 per cent On the other hand by limiting the studies to only those patients with otolaryngological signs one is apt to miss about half of the cases with patology as only 6 of our 12 patients had experienced otolaryngological signs

The relationship of the sphenoid and posterior ethmoid cells to the optic nerve has received much attention as direct extension of the inflammation to the optic nerve trunk is possible In a study of Weille & Vang (1953) 171 skull specimens were dissected and dehiscences of the bone of the posterior ethmoid cell in a near contiguity to the optic nerve were found in 2 cases and of the sphenoid sinuses also in 2 cases In our study there were no cases with involvement of the sphenoid sinuses Rapid improvement of the optic neuritis following intervention of the paranasal sinuses has been reported (Calvet et al 1967) The natural course of optic neuritis shows however rapid improvement without therapy

In our study 6 out of 12 patients with otoloryngological pathology were suggested to have multiple sclerosis This agrees with the general opinion of the etiology of optic neuritis (Walsh & Hoyt 1969) It is of special interest that 5 of the 6 cases with multiple sclerosis had definite inflammatory changes of the paranasal sinuses at the time of optic neuritis The association of multiple sclerosis and sinusitis has been reported before (Bossy & Jequier 1961) Rather than indicating direct involvement of the inflammation from paranasal sinuses to the optic nerve the sinusitis may indicate harbouring of the agent leading later to multiple sclerosis This agent may be a virus, as has been suggested by Gadjusen (1965)

Summary

X rays of the paranasal sinuses of 104 consecutive patients with optic neuritis have been reviewed Abnormalities were found in 11 per cent Purulent maxillary sinusitis was observed in 3 cases thickened mucous membrane in the maxillary sinus in 3 cases and maxillary sinues cyst in 3 cases No pathological change of the sphenoid sinuses were observed At the follow up examination X ray abnormalities were still present in 5 cases and in 2 of these there were also abnormalities of the nasal smears and bacteriological culturesã Six out of 12 cases with otolaryngological pathology had experienced signs at the time of the appearance of the optic neuritis In 1 case of the series the optic nerve involvement was attributed to paranasal sinus inflammation In 6 out of the 12 patients with X ray abnormalities neurological examination had disclosed evidence of multiple sclerosis 5 of these had definite inflammatory changes of paranasal sinuses at the time of the appearance of the optic neuritis

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The authors are grateful to C J Sjoblom M D for his expert advice

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Authors address

Haartmaninkatu 4 00290 Helsinki 29 Finland

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Authors address
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The Department of Experimental Ophthalmology
University Eye Clinic Lund Sweden

AUTOMATIC DETERMINATION OF THE RESOLVING POWER OF THE EYE

BY

C E T Krakau & G Stigmar

Abstract

A luminous test object randomly presented either as two parallel lines or as a rectangular band has been used as the stimulus pattern for an automatic determination of the resolving power of the eye

The effect of blurring of the test object on the resolving power has been investigated in a group of six experimentees

The relation between *resolving power vernier acuity and stereoscopic acuity* determined under the same conditions are discussed with special reference to the retinal light distribution

Key words *Visual acuity – Two line separation – –Resolving power – –Vernier acuity* – Stereoscopic acuity – Blurred target

Introduction

In previous studies we have reported on some factors influencing vernier and stereo acuities determined with a method which permits continuous recording of visual performances (Krakau 1967 Stigmar 1970 1971) The present paper

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is an attempt to apply *this type of examination* to another discriminative function *of the visual system* the resolving power of the eye (or two line separation)

The method of examination is based on the presentation of a test object (appearing on an oscilloscope screen) in one of two alternative views in a random way In a vernier (or stereo) situation the problem of producing two equivalent alternatives is simple i e the vernier off set to the right or left but for the task of two line separation some difficulties are involved

Suppose that one of our alternatives for testing *the resolving power is a test* object made up of two parallel and identical *luminous lines on a dark back* ground. *When the separation* distance between the lines is decreased the image of the lines gradually coalesce and finally they are superimposed on one another Therefore it is possible to make a correct judgement of two lines even beyond the true limit of resolution since the image of the two coalescent lines is perceived as wider and slightly brighter than a single one

This source of error in the determination of the limit of resolution with two lines (or two dots) as the test object has been pointed out by Selwyn (1948) Le *Grand (1967)* and *Ogle (1969)* Martin et al *(1950)* have *tried to get round* it in *experiments with* a double star *object by presenting a* single star of area equal to the sum of the areas of the other two as the other alternative However as noted by Westheimer (1965) and Le Grand (1967) even if the double star is not seen as separated the elliptic elongation of the image may suggest the presence of two stars and too low values of the resolving power will be obtained

Consequently when one alternative consists of a two line target the second alternative *must be made up in such way as to give no illegitimate clues like* those described if the object is to be suitable *for an automatic system of con* tinuous visual testing Therefore the width and luminosity of the second alternative must be adjusted so as to give a retinal image which cannot be distinguished from that of two confluent lines The purpose of the present paper is to describe how this can be achieved Some results of determinations of resolving power *will* be given when tested with unblurred and blurred targets

Method

The general procedure of the testing is identical with that of vernier testing (Stigmar 1970) The test target is generated *on an oscilloscope* screen and shown as successive views in one of two alternative shapes, chosen at random

One of the alternatives is two parallel lines (which may be screened off t points) In the present study the length of the two lines has been kept constar = 17 mm Since the examination distance = 3 000 mm the visual angle, sub tended by the length of the lines = 20 min arc The distance between the line is changed stepwise The ratio between two distances at consecutive steps is 1 5

The two line alternative is easily obtained from a square wave convenientl timed to the sweep frequency The other alternative is a rectangular luminou band the width of which is changed stepwise like the two line alternative Th luminous band has been achieved by modulating the luminous line with a tri angular wave of high frequency (40 kc) Efforts have been made to generate a homogenous luminosity over this surface

At testing, only one of the alternatives is shown at a time but the impres sion of size and luminosity remains sufficiently long to make it necessary t adjust both these qualities to a similar impression when seen from a sufficientl long distance This could be accomplished by making the luminous band abou 50 per cent wider than the distance between the lines at the same step

In previous papers (Krakau & Stigmar 1971, Stigmar 1971a) the influence o the contour sharpness of the target on vernier and stereo acuities has beer studied By means of a semi translucent screen at different distances in front o the oscilloscope screen it was possible to produce various degrees of degradation (blur) of the contour-sharpness

The same technique can be applied in order to change the contour sharpnes of the present target The light distribution across the test lines has been ana lysed in a similar way to the vernier target (Krakau & Stigmar 1971) Fig 1 shows examples of light distributions across unblurred and blurred targets of both the alternatives for some different separation distances (steps) between the lines The difference in luminance at the center of the luminous lines the dip *is defined in terms of contrast as* $\frac{a-b}{a}$ *(maximum minus minimum* value divided by maximum value cf Fig 1a)

The dip has been measured for eight different degrees of contour sharpness (w_0–w_7) and at different distances between the lines The results are presented in Fig 2 Each curve in the family corresponds to a fixed degree of blurring and shows the dip as a function of the distance between the two lines It is obvious that the dip is reduced and finally disappears when the lines approach each other The wider the light distributions the greater the line distance at effacing the dip

With the set up used in a previous study (Krakau & Stigmar 1971) a fair ap proximation of the light distribution of a single line blurred or unblurred is obtained by normal frequency function plus a constant The latter was found

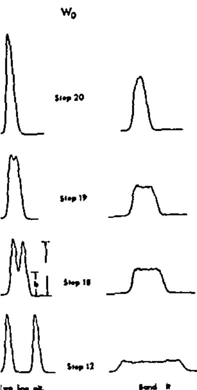


Fig 1a
Unblurred light distribution across the oscilloscope target. *Left* the two line alternatives four different distances (steps) between the lines *Right* corresponding band alternatives

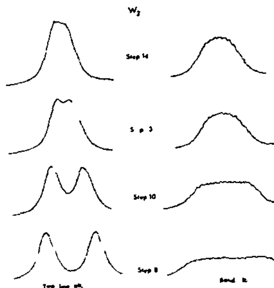


Fig 1b
Blurred target otherwise as in 1a.

to be 11 per cent of the total height of the maximum The properties of two superposed Gaussian functions are therefore relevant.

The function

$$f(x) = e^{-\frac{(x - x_0)^2}{2\sigma^2}} + k + e^{-\frac{(x + x_0)^2}{2\sigma^2}} + k \qquad (1)$$

is the sum of two identical distributions placed at $-x_0$ and x_0 and the constants $k = 0\,1\,5$ Since the constants do not influence the properties of the function in principle they are omitted for the moment. Fig 3 shows the function drawn

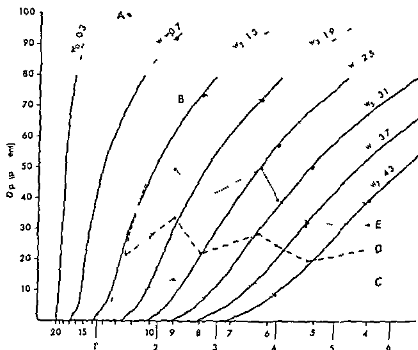


Fig 2

Dip values (in per cent ordinate axis) measured on the oscilloscope target versus the distance between the lines (2 x_0 *in steps and min arc* abscissa axis) full drawn lines Each line *corresponds* to a fixed degree of blurring (half widths given at the top of each curve) *A* The points of the curve A are *mean* values for the group at all degrees of blurring B The curve B is constructed from the approximation normal function *plus constant* and *should correspond* to curve w_ C and D *Dip of the retinal image* calculated on the *hypothesis that the* line spread function is $e^{-a/x/}$ a = 0 7 (C) a = 1 17 (D) E Retinal dip calculated on the hypothesis that the line spread function is a normal function half width 1 5 The values of C, D and E falling at 4 6 are based on the mean of two A values

for a few values of $/x_0/$ The standard deviation has been put = 1 Only the left part of the symmetrical curve is given When $/x_0/ > 1$ the compound distribution has two maxima and a minimum between them When $x_0 \leq 1$ the minimum is affaced and the two maxima coalesce With decreasing distance between the distributions (2 x_0) there is a displacement of the maxima towards the centre The curve of Fig 4 shows the position of the maximum x_m (ordinate axis) as a function of the distance x_0 We further note that the level of both a and b is increased when the distributions are approached (Fig 3)

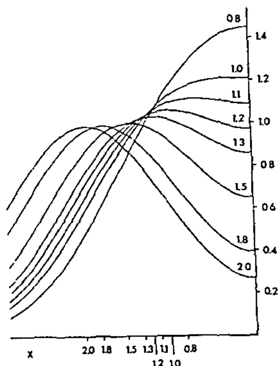


Fig 3

The sum of two identical normal curves placed at different distances from each other (only the left part of the symmetrical image is shown)

The dip defined by $(a-b)/a$ (cf Fig 1a) has been plotted as a function of the distance x_0 in Fig 5

Introduction of the constant k changes the dip by increasing the denominator by $\approx k = 0.25$ The value of a is but little higher than 1 (except when x_0 is small) and the dip values of Fig 5 are therefore reduced by a factor approximatively ≈ 0.8

The approximative expression for the blurred distribution (normal function plus a constant) is valid only in a limited range. Outside this the intensity slowly falls below the value of the constant to the very small values. Therefore, when the two lines are well apart the dip may reach values near 100 per cent The agreement between the dip values obtained from two superposed normal functions plus constants and those directly measured on the oscilloscope screen can

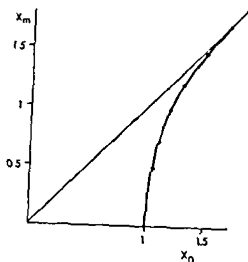


Fig 4
Position of the maxima (ordinate axis) as a function of the distance between the normal functions ($2x_0$ abscissa axis)

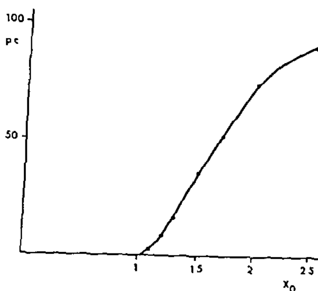


Fig 5
Dip for two superposed normal functions as a function of the distance between them ($2x_0$)

therefore be satisfying only when the lines are fairly near each other (reckoned in relation to the line width) In Fig 2 a dip curve calculated from the relation

normal function plus constant has been drawn (curve B) with the parameter (s d) calculated from the blurred line of the half width = 1.3 From Fig 5 in a previous paper (Krakau & Stigmar 1971) we get the ratio half width to s d = 2 54 and the s d for the constructed curve should then be 0 51 The agreement is found to be satisfying up to a dip of say 75 per cent. The constructed curve then does not reach a higher dip value than about 80 per cent (due to the constant) whereas the true dip increases further (due to the fading of the intensity distribution outside the values covered by the approximation normal function plus constant) In consequence the constant has been omitted in the calculations of the dip of the retinal image (v i) when the lines are well apart ($x_0/\sigma > 3$)

Estimation of the probability of correct interpretation of an object

The probability p_i of interpreting correctly a specific target E_i is made by one component of real seeing p and one of pure guessing p^g For the two alternative targets $p^g = 0.5$ For symmetrical types of targets we suppose that $p = p^v + (1 - p_i) p^g = 0.5$ p + 0.5 (Barany 1946 Krakau 1967)

For the asymmetrical alternatives two lines a band the interpretations seem to occur somewhat differently all doubtful interpretations being taken as the band alternative. Thus the two line alternative is interpreted correctly with probability p_i and the band alternative always *correctly Since the two alternatives are presented with* equal probabilities we get $p_i = 0.5$ p + 0.5 as before In a few series performed with recording of the type error all errors were of the type two lines seen as one and none of the type one line seen as two which supports the assumption made

The probability of making a step towards a more difficult object $p_{i,i\ 1}$ is p_i^3 (since three correct interpretations are needed) Hence the probability of taking a step from the i th object E_i towards the next more difficult one is related to the true probability of seeing the i th object correctly by

$$P \quad i \quad 1 = (0.5 p + 0.5)^3 \qquad ( )$$

P_i 1 is estimated from the number of transitions from the level i to i + 1 (n 1) and to i - 1 (n 1) by

$$P \quad 1 = \frac{n_{i\ i\ \ 1}}{n_{i,i\ \ 1} + n_{i\ \ 1}} \qquad (3)$$

(ns dering that $n_{i\ i\ 1} = n$ $_{1\ 1}$ we note that $p_{m,m\ 1} > 0.5$ and that $p_{m\ 1\ m\ 2} < 0.5$ if n_m $_m$ 1 is the mode of the set $\{n\ \ i\ \ \ i\}$ *By making the steps small the object seen with* probability 0.5 can be approached arbitrarily near the one corres pond g to the mode n_m $_m$ 1 However the location of the mode is in fact not de termined very prec sely by the fairly coarsely spaced objects. Instead of making an inte pe lat on it has been preferred to use the mean of the distribution, which seems to be just fied since the distribution of the set $\{n\ \ i\ \ \ i\}$ as a rule appears symmetrical

Fr m the relat on ( ) we find that the probability of a transition = 0.5 corresponds to a probability of seeing p of approx. 0 €

Material and Results

Six experimentees with normal visual acuity at conventional testing by Monoyer's letter charts have been used Their refractions fall in the range from + 0 5 to – 0 5 They were tested binocularly with natural pupils and with full correction The results are given in Table I as mean values (in min arc and steps) range of mean values and mean and range of the dispersion of the individual performances when tested with blurred and unblurred targets The general procedure or the testing followed the same pattern as that used in other experiments in the present series (Stigmar 1970) Accordingly at each of the eight types of experimental sessions every subject was examined twice. The duration of a single session was five min

The trend of the acuity values is clearly towards lower acuities with increasing blurring of the targets For comparison the vernier and stereo acuities found by Stigmar (1971a) have also been drawn in Fig 6 Five of the six subjects are common to both groups

The dispersion of the values at each performance is smaller than that obtained at vernier and stereo testing if we reckon in steps and not in absolute measures

Discussion

Among the extensive literature on the resolving power of the eye there are relatively few reports concerning the discrimination of two luminous lines on a dark background With this type of test object Roelof (1918) Wilcox (1932)

Table I

Results of testing six subjects with two line separation at various degrees of blurring

	Mean (min arc)	Mean (steps)	Range (steps)	Dispersion (s d) mean steps	Dispersion range steps
w_0	1 5	11 4	10 2–12 9	0 60	0 86–0 80
w_1	2 8	9 1	7 5– 9 9	0 77	0 48–1 19
w_2	2 8	8 0	6 0–10 0	0 77	0 41–1 2[illegible]
w_3	3 7	6 3	5 1– 7 6	0 83	0 59–1 33
w_4	4 0	5 9	4 9– 7 0	0 92	0 61–1 48
w_5	4 6	5 1	3 8– 6 3	0 80	0 48–1 22
w_6	4 6	5 2	3 8– 7 2	0 86	0 58–1 21
w_7	5 7	4 0	2 6– 5 9	0 48	0 63–0 86

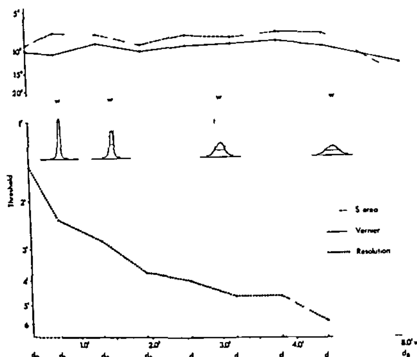


Fig 6
Comparison between vernier acuity stereoscopic acuity and two line separation for different degrees of bluring (abscissa axis)

and Fry & Cobb (1937) have found thresholds between 40 sec and 1 min This visual performance depends to some extent on the length of the lines Thus if the length is reduced the test situation approaches that of a two dot resolution where the limit of resolution varies between 1 7 and 3 5 (for ref see Le Grand 1967)

The two-line separation values obtained by the present method are of the same magnitude as those accepted by other authors which may be taken as an indication that secondary clues have not seriously influenced the determinations As seen in Table I the mean value for the unblurred targets falls at the line distance 1.5

The dip needed for resolution can be found by plotting the acuity mean values at different degrees of blurring into the diagram Fig 2 (curve V) A deeper dip seems to be needed when the target is unblurred than at high degrees of blurring

Material and Results

Six experimentees with normal visual acuity at conventional testing by Mon oyer s letter charts have been used Their refractions fall in the range from + 0 5 to – 0 5 They were tested binocularly with natural pupils and with full correction The results are given in Table I as mean values (in min arc and steps) range of mean values and mean and range of the dispersion of the indi vidual performances when tested with blurred and unblurred targets The general procedure or the testing followed the same pattern as that used in other experiments in the present series (Stigmar 1970) Accordingly at each of the eight types of experimental sessions every subject was examined twice The duration of a single session was five min

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w_0	1 5	11 4	10 2–12 9	0 60	0 86–0 80
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w_5	4 6	5 1	3 8– 6 3	0 80	0 48–1 02
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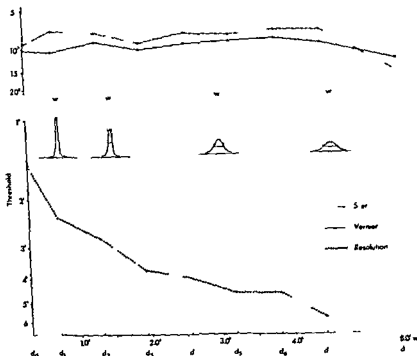


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The dip needed for resolution can be found by plotting the acuity mean values at different degrees of blurring into the diagram Fig 2 (curve A) A deeper dip seems to be needed when the target is unblurred than at high degrees of blurring

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w_3	3 7	6 3	5 1– 7 6	0 83	0 59–1 33
w_4	4 0	5 9	4 9– 7 0	0 92	0 61–1 48
w_5	4 6	5 1	3 8– 6 3	0 80	0 48–1 [illegible]2
w_6	4 6	5 2	3 8– 7 2	0 86	0 58–1 21
w_7	5 7	4 0	2 6– 5 9	0 78	0 63–0 86

The performance is recorded as a step shaped graph with undulations covering a number of steps When the vernier acuity is tested the range generally amounts to 6–8 steps whereas the two line separation as a rule shows only minor fluctuations It sometimes happens that for the whole period only two adjacent sizes of object are visited The whole set of objects with probabilities of seeing from those always correctly interpreted (p = 1) to those only guessed (p = 0) may thus be included in the space of one step i e for instance from 1 to 1 12

It is often remarked that the vernier acuity is much higher than the resolving power It has then to be taken into account that the latter consists of two parts an optic one which is determined by the limit (L) in the line distance where a small (infinitesimal) increase gives an infinitesimal saddle of the retinal distribution and secondly a physiological part which corresponds to the additional distance (x) at which a correct interpretation is obtained with probability p(x + L) Evidently since physiological mechanisms have no clue to correct interpretation without a saddle $p(a) = 0$ if $a \leq L$ If the physiological performances of vernier and two line separation are to be compared it would be preferable to consider the ranges of the two acuities (or even the range from zero to the all correct level for the vernier) we may find values like 5 8 for vernier and as mentioned 12 for resolving power By this approach these two acuities have been brought closer to each other

There is a parallel to the difference in blurring sensitivity of vernier and resolution in another respect namely dependence on luminosity It is well known (cf Hecht 1927) that resolving power in a wide range increases with increased luminosity (i e the relative distribution of light in the test object is unchanged when the total light emission is varied) This is also true for luminous targets on a dark background but in this case the acuity reaches an optimum at a certain intensity According to some authors vernier acuity does not seem to be so dependent on the luminosity of the target (Laurens 1914 French 1920) This view is also supported by investigations in the present series (Stigmar 1971b)

When testing the vernier and stereo acuities a set of probabilities of correct interpretation which are functions of the disparity is obtained Little is known about the operations performed retinally or at higher level to estimate this disparity or displacement within the test object The displacement is determined by the relative positions of the distribution maxima for these parts and this distance is invariant at changes in the distribution such as blurring or luminosity At the types of acuity mentioned there is no *a priori* necessity for lowered level of performance at blurring etc.

Accordingly up to a certain limit the vernier and stereo acuities are not

Mainly due to diffraction the original light distribution of the object undergoes a certain degradation, comparable to some blurring of the retinal image.

This inevitable effect may be expressed by means of the so called line spread function which is the light distribution across the retinal image of a thin (luminous) line. With the knowledge of this function which we may denote g(x) one can calculate the retinal distribution when the double line target distribution (f(x) cf eq. (1)) is known by forming the convolution of f and g

$$F(x) = \int_{-\infty}^{\infty} f(x-\xi)\, g(\xi)\, d\xi \qquad (4)$$

The actual line spread functions characterizing the eyes of our experimentees are not known but several authors have determined expressions for normal human eyes which might be applied as approximations. Fry & Cobb (1935) have suggested a Gaussian function. The dispersion measure needed for the adaptation of this function can be obtained from the line spread functions given by Campbell & Gubisch (1966). The half-width value which can be measured at normal pupillary size (say 3.5 mm) is about 1.5. Assuming the distribution to be Gaussian (which is of course an approximation) the s.d. should be put 0.63. The dip values of F(x) calculated by means of this normal function and the target distributions (eq. 4) have been plotted into the Fig. 2 curve E.

The investigations of Flamant (1955) and Rohler (1962) have resulted in a different expression for the line spread function namely an exponential curve of the form $g(x) = e^{-\alpha|x|}$ where x is expressed in minutes of arc. The value of α is estimated to 0.7 by Flamant and to 1.17 by Rohler.

The dip values of F(x) obtained with the exponential types of line spread function have also been plotted into Fig. 2 curves C and D respectively.

The calculated retinal dip values vary considerably with the type of line spread function applied. Obviously the retinal dip values cannot be estimated without a precise knowledge of the line spread function of the experimentees. The general trend is clear however that the imaging of the eye reduces the dip value of the unblurred and slightly blurred images strongly whereas the dip values are only moderately influenced when the images are highly blurred.

This implies that if the resolving power of an eye is reduced for optical reasons such as opacities or abberrations the most abnormal values should be expected for unblurred targets whereas nearly normal performances might be found when the strongly blurred images are used. On the other hand in cases of visual defects from reduced capacity to discriminate intensity differences an impaired resolution might be expected also at blurred images. The first part of this supposition is easily verified by studying the effect of defocusing lenses or slightly opaque screens.

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Authors address
Professor C E T Krakau or Dr G Stigmar
The Department of Experimental Ophthalmology University Eye Clinic
Lund Sweden

influenced by blurring or, in a certain range by changes in luminosity

This is, however the case in resolving power When testing this faculty we obtain a set of probabilities corresponding to various distances between the lines More directly these probabilities depend on the "dip" presented and the latter depends not only on the distance between the lines but also on the blurring of the lines It is well established from studies of the intensity discrimination (Hecht et al 1938) that the detectable contrast ($\Delta I/I$) decreases with increasing luminosity (I) Consequently the probability of detecting a dip of a certain magnitude should vary with luminosity

The probability (p) of detecting a dip is thus a function of dip and of luminosity The dip itself is a function of line distance and of blurring The dependence between the variables is clear by writing symbolically p (dip (line dist blurring) luminosity) Obviously the resolving power must be influenced by blurring and luminosity, which is confirmed in our experiments

Acknowledgments

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COLOURED LENSES AND CAR DRIVING

To the Editor –
Berggren (1) discussed some effects relating to the use of coloured glasses in car driving and cited some of the previous work on the subject A few points arising from his paper are discussed here

1 Berggren claimed that a percentage absorption quoted for a coloured lens suggests an even transmission and is misleading if that is not the case The absorption of a lens is the complement of the luminous transmittance (or luminous transmission factor B S 3521 1962) an internationally recognized *quantity that relates only to the fraction of incident luminous flux transmitted* by the lens regardless of the variations in the spectral transmittance values of the lens The use of percentage absorption has been criticized (2) but only on the grounds of possible confusion with the luminous transmittance expressed as a percentage

2 Berggren tested the effect on Nagel anomaloscope readings when subjects observed through coloured lenses Descriptions of at least two similar experiments have been available for some time (3 4) Such experiments would be more valuable if evidence could be produced to show that results obtained under anomaloscope conditions (small bright field with extensive dark surround) have any validity at all for conditions of an extensive daylit scene in which chromatic adaptation modifies the appearance of the scene viewed through coloured lenses In this type of experiment the change in mean settings is entirely calculable if the anomaloscope s spectral energy distributions and the lens transmittance values are known *so that it is possible to avoid using* experimental subjects at all Alternatively if the test is intended to give some idea of a lens transmittance curve then the anomaloscope s spectral energy distributions should be taken into account The increases in ranges of adjustment found when Berggren tested the denser glasses are probably a direct result of the *reduced luminances of the* anomaloscope *test fields* There seems to be no mention of how these luminances compare with those occurring when sunglasses are normally worn Certainly when coloured lenses cause a colour normal s

Ophthalmic Specialty Residency Training

The division of Ophthalmology of the State University of New York Downstate Medical Center will offer one year clinical fellowships beginning July 1 1972 in ocular motility retinal diseases and surgery glaucoma neuro ophthalmology and corneal surgery The applicant may in some circumstances elect six month periods in two areas. These fellowships are open to applicants who have completed three or more years of residency training in ophthalmology Stipend is currently $ 16 000 per annum Please make inquiry to Dr Richard C Troutman Professor Division of Ophthalmology Department of Surgery State University of New York Downstate Medical Center 450 Clarkson Avenue Brooklyn New York 11203

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red green setting on the anomaloscope to be shifted towards the protanomalous or deuteranomalous ranges this does not mean that the colour normal wearing the lenses sees like a colour defective, because it is well known that passive colour filters cannot fully simulate partial or complete dichromatism

3 Berggren stated "Only grey glasses show an even absorption This is true but the implication that it applies to *all* grey glasses is not It is possible for glasses with several absorption bands spaced across the visible spectrum to appear indistinguishable from spectrally neutral grey lenses because of the phenomenon of metamerism Apparent greyness of a lens therefore is not sufficient to guarantee spectral neutrality

4 Berggren tested the ability of subjects to interpret pseudoisochromatic plates observed through coloured lenses Experiments like this in method and value have been described perviously (5 6 7) Again it would be worthwhile to have some justification for relating the changes in test scores to changes in drivers performance of specific tasks in driving Unfortunately since pseudoisochromatic plates are designed to give certain chromaticity – luminance differences to normal and colour defective observers under standard conditions of illumination the test scores are of doubtful validity because these conditions are effectively changed by observing through coloured lenses Unless the spectral properties of the lenses illuminant and plates are known then one cannot even guess what the results might mean

5 Berggren expressed disappointment that proposals for the use of form (shape) signals in road traffic had not been put into practice They have been in use in Switzerland however (8) and are used to some extent in Australia These proposals usually give insufficient attention to the fact that shapes other than circular may reduce the signal intensity an undesirable result because traffic lights of types in widespread usage are already inadequate in intensity (9) Furthermore most difficulty in recognizing signal colours is likely to occur at distances where form signals of practicable size would be difficult to distinguish especially in the case of drivers whose visual acuity was at or near the legally acceptable minimum for driving One of the references cited in favour of form signals (10) describes experiments apparently assisted by a form signal manufacturer This reference also omits mention of several important prior investigations and contains the following statement "Because of a difference in transmission of the different [traffic signal] lenses (0 04 for the red 0 02 for the green and 0 4 for the yellow) by simply doubling the intensity of all lights the green would be increased five times as much as the red the yellow ten times as much as the red Even allowing that 0 02 may have been a misprint for 0 2 this statement is at variance with basic concepts of physical and physiological optics notwithstanding that distant red signals always appear more intense than basic theory suggests (11) In any case the introduction of form signals does not appear to be as important as the need

to suppress phantom indications in signals since it is possible for phantom *signal intensities* to exceed those of genuine indications (12 13)

6 Berggren stated that The use of symbols and lines as remote as possible *on the spectrum* in street lights flashing signals and rear red lights would lead to much less confussion This proposal is unacceptable since the colours *to be* used would presumably be deep red violet green and white It is physically impossible to have deep red and violet filters with sufficiently high luminous transmittance to ensure adequate intensity of the signals with the types of lamps used in traffic signal heads at present Violet has been rejected as a signal colour by many competent investigators and in any case considera tion of the iso colour zones for dichromats (14) indicates that remoneteness of colours in the spectrum does not guarantee that the colours will be distinguish able by dichromats The present CIE coloration limits for traffic signals (15) are about as good as is practicable for a four colour system to be used by colour defectives as well as normals

7 Berggren s reference list does not include any papers dealing with what is probably the major problem in effects of coloured glasses in driving nor with its solution Coloured lenses can change the apparent intensity of signal lights with consequent changes in the driver s signal recognition performance These effects have been discussed quantitatively (16 17) and mention of the theory has been made in other papers (2 18–21) all of which were published prior to submission of Berggren s manuscript Briefly the reaction time and recognition probability for a red traffic signal is determined by the ratio of signal to background luminance (22) For signals viewed through coloured lenses differential transmission of red and white light will alter the appar ent ratio of signal to background luminance causing a calculable change in the observer s performance The differential transmission of a lens is given by the signal visibility factor here called R which can be calculated from the transmittance curve of the lens basically it is just the ratio [transmission of red light/luminous transmittance] A spectrally neutral lens has $R = 1$ a green *lens has* $R < 1$ *and a brown lens* $R > 1$ Performance losses were used (16) to set arbitrary limits on acceptable values of R for general purpose use such as driving it *was proposed that lenses should have* R within the range 0 8 to 1 ? and for specfic tasks such as aircraft ship or locomotive operation the range proposed was 0 9 to 1 1 Minus *blueness of the* lenses was also considered undesirable since yellow lenses can remove all of the residual hue discrimination of dichromats (16)

More recent publications (?3–?5) describe some further work on the subject Of particular interest is the result that ratios of red *to green transmittances* are not well correlated with R so that anomaloscope tests do not give an accurate measure of the effect that coloured lenses will have on the perception of red traffic signals (3) Another result is that an Australian Standard for

Sunglass Lenses AS 1067 1971, has recently been issued this specifies an R value of between 0 70 and 1 40 for general purpose sunglass lenses and between 0 85 and 1 15 for specific purpose lenses Finally although Berggren stated that sunglass lenses should absorb infra red radiation which is reasonable (26) he failed to note that of the two types of lenses that were neutral according to his anomaloscope tests one type (the polarizing lenses) transmits almost the maximum possible amount of near infra red radiation (27, 28)

Barry A J Clark
Defence Standrads Laboratories Department of Supply
Melbourne Australia

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Reply to BARRY A J CLARK

To the Editor –

Mr Clark has perhaps unintentionally misunderstood my article The basic purpose of my paper stated in the introduction was to draw attention to the present traffic regulations in Sweden which do not allow colour defective bus drivers The validity of this demand was questioned since there is no restriction against the use of coloured glasses in Sweden Some common sunglasses were therefore examined with the colour vision tests used in the examination of bus drivers and it was shown that the ability to perform these tests was influenced

It was not my intention to enlarge my paper to a full discussion of technical aspects of coloured glasses and car driving A discussion of all the points brought forward in your letter to the editor is not possible within the space allowed for answering the letter

Lennart Berggren
Umeå Sweden

From the Laboratory of Clinical Neurophysiology Rigshospitalet Copenhagen and the Eye Department Rigshospitalet Copenhagen (Former Head H Ehlers)

ENDOCRINE OPHTHALMOPLEGIA

Is it due to myopathy or to mechanical immobilization?

BY

SVEND FAURSCHOU JENSEN

Endocrine ophthalmoplegia is often associated with thyrotoxicosis Only nine of the fifty patients reviewed by Brain (1959) had neither been nor were thyrotoxic One may assume that the paresis results from thyrotoxic myopathy So far electromyographic study of the external eye muscles has not afforded a consistent answer to this question Some workers have interpreted the interference pattern of the electromyogram during maximum effort as a sign of myopathy (Schultz et al 1960 Esslen & Papst 1961 Huber 1963 Magora et al 1968) *others as a sign of mechanical obstacle to the motility of the eye ball* (Breinin 1967) The occurrence of an interference pattern cannot however serve to distinguish between these possibilities The present study was undertaken to investigate whether endocrine ophthalmoplegia is accompanied by other electromyographic changes compatible with myopathy

Material

There were 18 patients 13 females and 5 males (36 to 73 years of age average 57 *years)* *At the time of the investigation* 11 of the patients showed evidence of thyrotoxicosis The remaining 7 had previously exhibited signs of disturb

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Reply to BARRY A. J. CLARK

To the Editor –

Mr. Clark has perhaps unintentionally misunderstood my article. The basic purpose of my paper stated in the introduction was to draw attention to the present traffic regulations in Sweden which do not allow colour defective bus drivers. The validity of this demand was questioned since there is no restriction against the use of coloured glasses in Sweden. Some common sunglasses were therefore examined with the colour vision tests used in the examination of bus drivers and it was shown that the ability to perform these tests was influenced.

It was not my intention to enlarge my paper to a full discussion of technical aspects of coloured glasses and car driving. A discussion of all the points brought forward in your letter to the editor is not possible within the space allowed for answering the letter.

Lennart Berggren
Umeå, Sweden

Table I

Electromyographic findings in 18 patients with endocrine ophthalmoplegic exophthalmus

No	Age	Sex	Paresis	Duration of disease	Muscle	Ampl full effort µV[2]	Mean durat msec	Mean ampl µVs[3]	% Polyphas	Number of pot
Without signs of thyrotoxicosis										
11517	39	F	severe	2 yrs	rect sup	240	2.5	93	5	20
11179	4	F	slight	1 yr 4 mo	rect sup	240	2.9	83	13	15
11548	52	F	severe	1 yr 3 mo	rect sup	300	2.8	124	0	21
11731	47	M	moderate	5 mo	rect lat	400	2.6	89	11	27
1184	44	F	severe	5 mo	rect sup	400	2.5	109	0	24
12475	79	M	severe	6 mo	rect sup	200	2.5	110	0	19
12003	65	F	severe	4 mo	rect sup	240	2.6	84	2	43
12807	68	F	slight	2 yrs	rect med	240	2.7	106	17	35
10 53	36	F	severe	10 mo	rect sup	400	2.3[4]	63	5	20
9340	65	M	severe	8 mo	rect sup	140	2.1[4]	57	5	21
1 374	47	M	severe	4 yrs	rect sup	250	2.3[4]	10	0	27
With signs of thyrotoxicosis										
1101	48	F	moderate	2 yrs	rect sup	500	2.7	196	4	25
10 68	44	F	severe	2 mo	rect sup	300	3.0	80	0	19
10139	63	M	severe	1 yr 8 mo	rect sup	300	2.5	96	4	24
12750	46	F	severe	2 yrs	rect sup	240	2.8	87	3	35
13428	51	F	severe	2 yrs	rect lat	2 0	2.6	76	0	25
13341	58	F	severe	2 yrs	rect lat	200	2.9	115	6	34
14170	38	F	severe	1 yr	rect lat	240	2.9	101	0	23

1 Normal 20 muscles amplitude at *full effort 360 µV* S.D. 101 µV mean duration 2.5 msec S.D. 0.1 msec mean amplitude *102 µV* S.D. 12 µV. *The standard* deviation (S.D.) gives the variation from subject to subject. Incidence of polyphasic potentials 3.4 per cent

2 In all patients interference pattern of discharge

3 Peak to peak amplitude of randomly sampled motor unit potentials

4 Suggestive of myopathy ($p < 0.05$)

ances of the thyroid function either an elevated basal metabolic rate, an elevated protein bound iodine, or an increased uptake of I^{131} The patients had paresis of one or more ocular muscles in 14 so severe that there were only slight rocking movements of the eye ball or none at all when active or passive movements were attempted (Table I)

Method

The concentric electrode developed for recording from the eye muscles its insertion the recording equipment and the electromyographic findings in normals have been described (Laurschou 1971) The criteria used were the same and concerned average duration and amplitude of motor unit potentials incidence of polyphasic potentials the pattern of discharge during maximum effort and its amplitude The number of different motor unit potentials recorded in each muscle is given in Table I The electrode had a leading off area of 0 015 mm In 10 patients recordings were also obtained from the brachial biceps muscle using a concentric electrode with a five times larger leading off area

Results

In 15 patients the mean duration of the motor unit potentials was normal Interference occurred during maximum effort and the amplitude of this pattern was normal (Table I) In three patients (with signs of thyrotoxicosis) the duration of the potentials was reduced by 38 and 45 per cent An increased occurrence of polyphasic potentials (> 12 per cent) was observed in one case (17 per cent) Clinical and electrophysiological signs of thyrotoxic myopathy of skeletal muscles were absent the duration and amplitude of the potentials in the brachial biceps muscle were normal in the 10 patients examined Six of these patients showed signs of thyrotoxicosis

Discussion

The electromyographic findings reported in this study demonstrate that endocrine ophthalmoplegia was usually not accompanied by electrophysiological signs of myopathy not even when the paresis was so severe as to amount to

Table I

Electromyographic findings [illegible] 18 patients with endocrine ophthalmoplegia [illegible][1]

No	Age	Sex	Paresis	Duration of disease	Muscle	Ampl full effort μV[2]	Mean durat msec	Mean ampl μV[3]	% Polyphasic	Number [illegible]
With signs of thyrotoxicosis										
11317	35	F	severe	2 yrs	rect sup	240	2.5	33	5	20
11178	54	F	slight	1 yr 4 mo	rect sup	240	2.3	83	13	15
11[illegible]48	52	F	severe	1 yr 3 mo	rect sup	300	2.8	124	0	21
11731	4	M	moderate	5 mo	rect lat	400	2.6	69	11	27
1181[illegible]	44	F	severe	5 mo	rect sup	400	2.5	109	0	24
12475	[illegible]3	M	severe	6 mo	rect sup	200	2.5	110	0	19
12003	65	F	severe	4 mo	rect sup	240	2.6	84	2	43
12507	68	F	slight	2 yrs	rect med	240	2.7	106	17	35
107[illegible]8	30	F	severe	10 mo	rect sup	400	2.3[4]	63	5	20
9946	65	M	severe	8 mo	rect sup	140	2.1[4]	57	5	21
12574	4	M	severe	4 yrs	rect sup	250	2.3[4]	105	0	27
Without signs of thyrotoxicosis										
11035	48	F	moderate	2 yrs	rect sup	500	2.7	126	4	25
10568	44	F	severe	2 mo	rect sup	300	3.0	80	0	19
10933	63	M	severe	1 yr 8 mo	rect sup	300	2.5	96	4	24
12750	46	F	severe	2 yrs	rect sup	240	2.8	87	3	35
13428	[illegible]	F	severe	2 yrs	rect lat	250	2.6	76	0	25
13341	58	F	severe	2 yrs	rect lat	200	2.9	115	6	34
141[illegible]0	38	F	severe	1 yr	rect lat	240	2.9	101	0	23

1 Normal 20 muscles amplitude at full effort 360 μV S.D. 101 μV mean duration 2.5 msec S.D. 0.1 msec mean amplitude 102 μV S.D. 12 μV. The standard deviation (S.D.) gives the variation from subject to subject. Incidence of polyphasic potentials 3.4 per cent

2 In all patients interference pattern of discharge

3 Peak to peak amplitude of randomly sampled motor unit potentials

4 Suggestive of myopathy ($p < 0.05$)

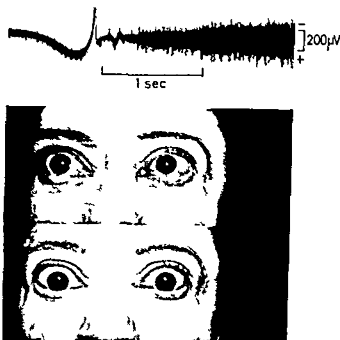


Figure 1
Endocrine exophthalmic ophthalmoplegia without electromyographic signs of myopathy Pt L P (11845) female 44 years old for the past 5 months severe paresis of the elevator muscles The upper picture shows the position of the eyes during maximum effort to look up when wrinkling of the forehead was absent The protein bound iodine was increased to 11 4 μg/100 ml Electromyography of the right m rectus superior (above) showed an interference pattern of normal amplitude during full effort (360 μV)

complete immobilisation of the eye One might argue that the duration of the potentials in the external ocular muscles is normally so short that further shortening in myopathy would not manifest itself However the duration was shortened in 3 of 18 patients and in 9 patients with ocular myopathy I have found an average shortening of the duration of 23 per cent and a reduction in amplitude of 37 per cent

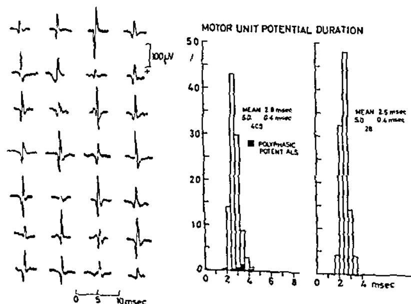
What is then the cause of the paresis of the ocular muscles? In dysthyroid ophthalmoplegia histological examinations showed an inflammatory reaction with oedema in the interstitial tissue of the ocular muscles without changes in the muscle fibres themselves (Kroll & Kuwabara 1966) The explanation of the paresis must then be immobilisation due to the increased volume of the interstitial space The shortened duration found in 3 of my patients might be secondary to the oedema A similar mechanism was assumed by Bremin (1962) who did not however establish whether the duration of the potentials was shortened or not

There are several differences between endocrine ophthalmoplegia and thyro

toxic myopathy Although thyrotoxic myopathy is accompanied by no or only negligible histological changes (Hed et al 1958 Harvard et al 1963 Ramsey 1966) there are electromyographic changes with a reduction in duration and amplitude of the potentials (Sanderson & Adey 1952 Yates 1963 Ramsay 1965 Vilppula & Buchthal 1970) Endocrine ophthalmoplegia may persist after the patient has become euthyroid whereas thyrotoxic myopathy of skeletal muscle is reversible both clinically and electrophysiologically Since myopathy is found in 80 per cent of the patients with thyrotoxicosis (Ramsay 1965) it is surprising that none of the 10 patients examined had electrophysiological signs of myopathy in the brachial biceps muscle

Summary

The purpose of the present study was to ascertain whether the paresis in endocrine ophthalmoplegia is due to myopathy or to mechanical immobilisation Electromyography of the external eye muscles in 15 of 18 patients was normal



Figure

Motor unit potentials from m rectus superior (pt no 11845 Fig 1) The *histogram to the right* shows the duration of the potentials to the left the duration of motor unit potentials in 10 normal muscles

even when the eye ball was nearly or completely immobilized The parameters measured were the average duration and amplitude of motor unit potentials the incidence of polyphasic potentials the pattern of discharge during maximum effort and its amplitude Three patients showed electromyographic signs of myopathy There were no clinical or electromyographic signs of thyrotoxic myopathy in the skeletal muscles The normal electromyogram found in 15 patients indicates that paresis was due to immobilization of the eye by interstitial oedema in the muscles rather than to myopathy The slight signs of myopathy in three patients were presumably secondary to the interstitial changes

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14 *Vilppula G & Buchthal F* Cit from F Buchthal Electrophysiological abnormalities in metabolic myopathies and neuropathies Acta neurol scand 46 suppl 43 129–176 1970

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From Institute for Experimental Medical Research
Division of Immunology (Head Docent Morten Harboe M.D.)
University of Oslo Ulleval Hospital Oslo

IMMUNOELECTROPHORESIS OF EXTRACTS FROM BOVINE CORNEAL EPITHELIUM USING ANTISERA SPECIFIC TO INDIVIDUAL PROTEIN FRACTIONS

BY

BJØRN BERGER

Previous immunoelectrophoretic studies on water soluble antigens from bovine corneal epithelium have been performed with antisera produced by immunization with crude extracts of the epithelium. These antisera react with various components of the corneal epithelium (see Faure 1964).

Recently a technique was described for agarose gel electrophoresis of proteins extracted from bovine corneal epithelium. Thirteen protein bands were identified in addition to a prominent electrophoretically heterogeneous protein fraction and a sharp band intensely stained by the periodic acid Schiff (PAS) reagent (Berger 1969). In the original investigation the technique was used for analytical purposes but is was developed with a view to possible use in the preparation of individual protein fractions from bovine corneal epithelium. It was later demonstrated that the method could be used for preparative purposes on a small scale which was suited to the rather small amounts of protein extractable after isolation of bovine corneal epithelium. It thus appeared possible to produce antisera against individual protein fractions from bovine corneal epithelium.

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even when the eye ball was nearly or completely immobilized The parameters measured were the average duration and amplitude of motor unit potentials the incidence of polyphasic potentials the pattern of discharge during maximum effort and its amplitude Three patients showed electromyographic signs of myopathy There were no clinical or electromyographic signs of thyrotoxic myopathy in the skeletal muscles The normal electromyogram found in 15 patients indicates that paresis was due to immobilization of the eye by interstitial oedema in the muscles rather than to myopathy The slight signs of myopathy in three patients were presumably secondary to the interstitial changes

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from about 60 mg per ml to about 50 mg per ml The precipitated protein was carefully washed to be used for immunization as described below

Precipitation by trichloroacetic acid

Proteins in extracts of bovine corneal epithelium were precipitated as follows The extract was diluted with phosphate buffered (pH 7 4) saline to a protein concentration of about 5 mg per ml and added to an equal volume of 20 % trichloroacetic acid After incubation at room temperature for 10 minutes the mixture was centrifuged at 3 000 rpm for 30 minutes at 4° C The supernatant was pipetted off and dialyzed at 4 C for 48 hours against phosphate buffered saline The sample was then concentrated it was lyophylized and subsequently dissolved in distilled water to yield a solution with the same volume as the original extract

Electrophoresis

Electrophoresis was carried out at pH 8 6 and 6 2

Electrophoresis was carried out in 0 75 % agarose gel (Agarose Behringwerke AG Marburg/Lahn Germany) containing a barbiturate buffer of pH 8 6 and ionic strength 0 02 The details of the method have been described previously (Berger 1969) A rectangular groove measuring 9 × 0 8 mm was cut ? cm from the cathodal side of the glass plate This groove was used for the application of a newly prepared extract of bovine corneal epithelium containing about 60 mg protein per ml During electrophoresis the application groove usually remained full of fluid which was required for optimal separation Occasionally there was some overflow on the anodic side of the application groove these plates were discarded A part of the gel was stained with Amido Black as described previously (Berger 1969) to identify the various protein bands Corresponding segments of the remaining part of the gel were cut out In some instances these segments were used directly for immunization of rabbits and guinea pigs as described below In other experiments protein was eluted from individual segments to be used for absorption of antisera.

Various brands of agarose were tried for electrophoresis They behaved differently but agarose from Behringwerke gave the best separation in the regular technique It was observed that when Seravac agarose (Miles Seravac Ltd Maidenhead England) was used for electrophoresis the application groove usually dried up during electrophoresis and that the protein fraction termed fraction No 8 could not be eluted from this type of gel

Protein was eluted from the gel by placing it in a tube containing a mesh at the bottom by centrifugation at 2 000 rpm for 20 minutes at 4 C, the gel remained in this tube while the protein containing liquid was forced out of the

The purpose of the present work was to produce specific antisera against individual protein fractions of bovine corneal epithelium Such antisera might then eventually be used as reagents to study the distribution of the various antigens in bovine corneal epithelium compared with other tissues

Material and Methods

Corneas

The corneas were collected and the epithelium prepared and stored as described previously (Berger 1969) After extraction of proteins by ultracentrifugation (Berger 1969) there was a marked tendency to spontaneous precipitation of protein from the water clear solution Since this might be due to denaturation of proteins some corneas were collected about 10 seconds after the death of the animal and compared with others collected about 15 minutes later In each instance the epithelium was isolated as soon as possible followed by immediate extraction of the protein No difference in behaviour of the proteins in the two types of extracts could be demonstrated by electrophoresis immunoelectrophoresis or in tendency to precipitate The corneas were therefore regularly obtained about 15 minutes after the death of the animals kept on ice and used for preparation of epithelium shortly thereafter

Protein extraction

For the majority of the experiments the proteins were extracted from bovine corneal epithelium by ultracentrifugation as described previously (Berger 1969) For some immunization experiments proteins were extracted by homogenization as described previously (Berger 1969) Ultracentrifugation was performed at 4° C in a Spinco preparative ultracentrifuge Model L50 equipped with a SW 39 head and a perspex tube constructed for protein extraction (Berger 1970)

Spontaneous precipitation of proteins from the extract of bovine corneal epithelium

Marked precipitation of protein occurred when the water clear solution resulting from extraction of bovine corneal epithelium by ultracentrifugation to a concentration of about 60 mg protein per ml was left at 37° C When the extract was left at 4° C precipitation occurred less rapidly After 3 hours at 37° C precipitation appeared to be complete since no further precipitation occurred after such an extract had been subjected to ultracentrifugation at 30 000 rpm for 30 minutes and then left at 37 C After such a complete precipitation" the concentration of protein in the extracts usually decreased

for immunoelectrophoresis were found to be different 0 75 % Behringwerke agarose gel containing barbiturate buffer of pH 8 6 with final ionic strength in the gel of 0 02 was used and the antibody trough was refilled once In these instances the protein concentration of the fresh extract was adjusted to 15 mg per ml by dilution with phosphate buffered saline (pH 7 4) at 4° C

To correlate the precipitin lines with the various bands obtained by electrophoretic separation immunological examinations were performed after regular agarose gel electrophoresis (Berger 1969) In these tests electrophoresis was carried out as shown in Fig 1 After termination of electrophoresis the antibody trough was cut parallel to the direction of electrophoresis the edge being 3 mm from the edge of the rectangular application groove

The plates were incubated in a moist chamber at room temperature for 48 hours before reading and photography Photography was performed using a dark field illumination and unstained slides All plates were kept in the moist chamber for one week washed in 0 9 % saline for 24 hours dried and stained with Amido Black The gels contained merthiolate (dissolved in distilled water) in a final concentration of 1 10 000 to prevent bacterial growth during this incubation

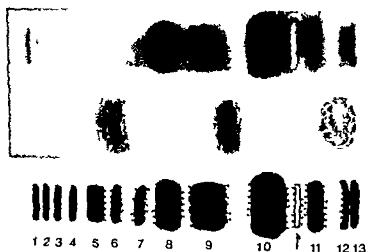


Fig 1

Protein zones obtained after electrophoresis of a fresh extract of bovine corneal epithelium prepared by *ultracentrifugation* A photograph of the slide is shown above, and a schematic drawing below Arrow marks application groove the anode is to the left The three reference points in the middle correspond to the positions of human serum albumin, human transferrin, and dextran

gel and sedimented at the bottom of another glass tube within which the gel containing tube had been placed The sample was then lyophylized in the cold and stored at 4° C (usually for less than 2 weeks) before use in absorption and other experiments

When extracts containing about 60 mg protein per ml were subjected to electrophoresis, the yield of protein in some fractions was quite low and a large number of electrophoreses would have to be carried out to obtain sufficient amounts of protein for the absorption experiments Experiments were then made using extracts concentrated to contain about 400 mg protein per ml Concentration was effected by lyophylization after removal of spontaneously precipitable protein The electrophoretic separation remained sufficiently good particularly with Seravac agarose gel larger amounts of protein were obtained and this procedure was found suitable for many of the absorption experiments

Electrophoresis was performed at pH 6 2 to separate the electrophoretically heterogeneous protein "fraction No 9 from the main protein fraction called "fraction No 10 At pH 8 6 the heterogeneous fraction was distributed all the way through from fraction No 6 to fraction No 13 This separation was performed at room temperature in 1 % Seravac agarose gel containing 0 17 molar phosphate buffer of pH 6 2 The concentration of phosphate buffer in the electrode vessels was 0 05 molar The application groove was placed 3 cm from the cathodal side of the plate and the electrophoresis was performed for 3 hours with a tension of 35V across the 8 2 × 8 2 cm plate Care had to be taken to refill the application groove to prevent it from drying which led to poor separation The sample used for this type of electrophoresis was obtained by diluting an extract of bovine corneal epithelium – from which precipitable protein had been removed by incubation at 37° C for 3 hours and subsequent ultracentrifugation – to a protein concentration of about 10 mg per ml After termination of electrophoresis the part of the gel located 5 to 10 mm on the cathodal side of the application groove was dissected out and eluted The eluate contained protein fraction 10 free of the protein with the electrophoretic heterogeneity

Immunoelectrophoresis

This was usually performed on 8 2 × 8 2 cm glass plates with 1 % Seravac agarose gel containing barbiturate buffer of pH 8 6 and ionic strength 0 05 The plates were kept for a few hours at 4° C in a moist chamber before use The samples were applied in a circular hole with a diameter of 3 mm the centre being placed 2 cm from the cathodal edge of the plate The antibody trough was 1 5 mm wide the distance from it to the edge of the application hole varied from 4 to 12 mm

When the antigens in fraction No 11 were tested the optimal conditions

animal Immunization was performed in intravenous *anesthesia with Nembutal* injections being made into the 20 footpads and intradermally at 20 sites in *the neck* the axillae and the groins Most animals received a booster injection without adjuvant 7 weeks later and 2 weeks later the animals were bled Serum was harvested and stored in small aliquots at -26° C Protein in fractions Nos 1 to 4 was given to guinea pigs using a *similar immunization procedure* Each guinea pig received gel segments suspended with 1/2 ml of complete Freund s adjuvant During ether anesthesia, injections were made in all foot pads at several intracutaneous sites and due to the large amount of gel some injections were also made subcutaneously

The animals immunized with fractions *Nos 1 to 4* did not produce detectable precipitating antibodies All the other animals produced potent antisera The electrophoretically heterogeneous protein with a marked tendency to aggregation and precipitation was a particularly potent antigen even before boosting potent antisera were obtained against this antigen Antibody of this specificity was found in all animals immunized with *electrophoretic fractions from No 8* to No 13 and in the rabbits immunized with the washed spontaneous precipitate In gel diffusion tests against isolated protein of the electrophoretic fraction No 9 all these antisera gave a precipitin line with reactions of identity when tested in parallel with an absorbed specific antiserum against fraction No *9*

Absorption of antisera

To be specific i e for each antiserum to precipitate with only one characteristic fraction of the extract the antisera had to be absorbed

Initially antibody activity against plasma proteins was absorbed out In most antisera precipitating antibodies against plasma proteins were found The plasma proteins with which the antisera reacted were of the same electrophoretic mobility as the gel segment cut out and used for immunization The antisera were absorbed with lyophylized normal plasma Controls for absorption were made by double diffusion in gel using the absorbed antisera in the centre well and various dilutions of plasma in the peripheral wells After absorption no precipitation was observed between the antisera and normal human plasma tested undiluted and in serial twofold dilutions up to 1 256

All antisera contained *antibodies against the electrophoretically heterogeneous* protein fraction of bovine corneal epithelium This is the protein fraction with marked tendency for spontaneous aggregation and precipitation The amount of protein required for absorption was determined by intrabasin absorption experiments in an immunoelectrophoretic test system The material used for absorption was usually protein eluted from gel segments containing some of the electrophoretically heterogeneous protein and another protein

Double diffusion tests

These were performed in 1 % agarose gel containing barbital buffer of pH 8 6 and ionic strength 0 05 A template was utilized consisting of a central circular well with a diameter of 3 mm surrounded by 6 similar wells of the same size Usually the distance between the centre of the central and peripheral wells was 9 mm in some experiments the distance was 5 mm For each antigen antibody system pilot experiments were performed to ascertain the optimal distance. The short distance was particularly useful for increasing the sensitivy of gel diffusion tests concerning the electrophoretically heterogeneous antigen Incuba tion photography and staining were as for immunoelectrophoresis

Immunization

Three types of materials were used for immunization (1) To produce polyvalent antisera reacting with various antigens in corneal epithelium four rabbits were immunized with a total extract of bovine corneal epithelium (2) To produce antisera against individual proteins in the extract animals were immunized with segments cut out from the agarose gel after electrophoresis The segments were cut out of the gel corresponding to distinct protein bands and subse quently mixed with 1 ml of complete Freund s adjuvant containing *Myco bacterium butyricum* (Difco Laboratories Detroit Mich cat no 0638–59) By repeated aspirations through a thin needle a stiff cream was formed which was very stable and optimal for immunization purposes (3) The extracts showed a marked tendency for spontaneous precipitation of protein when incubated at 37° C After such incubation precipitated proteins were washed repeatedly and then used for immunization

Rabbits were injected with crude extracts at five subcutaneous and intra muscular sites once weekly for 5 weeks each animal receiving a total of about 100 mg protein The first three injections were given with 1 ml complete Freund s adjuvant The animals immunized with segments cut out of the gel after electrophoresis received such segments prepared after 20 35 electrophoretic separations at each immunization The amount of protein given to each animal was calculated from the known total amount of protein in the extract the amount applied in the application groove of the agarose gel and the density curve described previously (Berger 1969) For fractions Nos 8 9 10 and 11 and for washed precipitated protein the amount of protein was 2 to 4 mg for the initial injection and 3 to 8 mg for the booster injection For fraction No 13 the amount given to each animal was about 0 6 mg for the initial injection and about 0 8 mg for the booster injection One to three rabbits were immunized with each fraction

Gel segments corresponding to fractions Nos 8 9 10 11 and 13 were given to rabbits The gel was mixed with 1 ml complete Freund s adjuvant for each

area of the gel consisted of fraction No 10 protein and some of the electrophoretically heterogeneous protein The absorption was made with lyophylized protein from one volume of eluate to two volumes of antiserum After absorption with this material the antiserum no longer precipitated with fraction 10 or fraction H The reactions of an absorbed antiserum are shown in Fig 3 This antiserum gave one precipitin line with a total extract of bovine corneal epithelium whose position corresponded to band No 8 after electrophoresis Precipitates denoted S on the drawing are apparently due to spontaneous precipitation in the gel since similar precipitates were observed when no serum was added to the antibody trough

Antisera prepared against electrophoretic fraction No 9

Fig 4 shows a typical immunoelectrophoresis with such an antiserum against a freshly prepared extract of bovine corneal epithelium containing about 60 mg protein per ml Two immunoprecipitates are seen denoted H and 10 on the schematic drawing The weak precipitate denoted 10 had a position corresponding to electrophoretic fraction No 10 In addition there is a long precipitin line termed H which extends from the position of fractions Nos 8 to 13 Precipitates termed S are apparently due to spontaneous precipitation of a protein fraction in the gel since similar precipitates were observed in gels where no serum was filled into the antibody trough

The antiserum was absorbed with lyophylized protein prepared by electrophoresis at pH 6 2 as described above By performing the electrophoresis at this pH antigen No 10 could be separated from the electrophoretically heterogeneous antigen and thus provide a material useful for absorption of

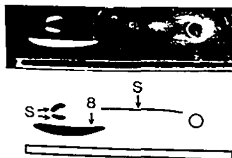


Fig 3
Photograph and drawing of immunoelectrophoresis in agarose gel of a fresh extract of bovine corneal epithelium against an antiserum absorbed to be specific against fraction No 8

against which contaminating antibodies should be removed In some cases lyophylized washed *aggregated protein was used for absorption* of unwanted antibodies against fraction No 9 When antisera were absorbed with proteins obtained by elution from defined segments after electrophoresis the proteins were eluted from gels as described previously, and used for absorption by mixing lyophylized protein with antiserum Controls were made by immuno electrophoresis against total extracts of bovine corneal epithelium of varying concentration to demonstrate reactivity against a single electrophoretic fraction

Experiments and Results

Antisera prepared against electrophoretic fraction No 8

A typical example of immunoelectrophoresis of a freshly prepared extract of bovine corneal epithelium with protein concentration 60 mg per ml against an unabsorbed antiserum of this kind is shown in Fig 2 Three immunoprecipitates are seen denoted 8 10 and H on the schematic drawing The points of the precipitates 8 and 10 closest to the antibody trough corresponded to the positions of bands Nos 8 and 10 after electrophoresis The immunoprecipitate denoted H covered the area from the position of fraction No 8 to fraction No 13 This extended line is typical of a reaction between antibody and the elec*trophoretically heterogeneous protein which has a strong tendency to precipitat* spontaneously from aqueous extracts of bovine corneal epithelium

For absorption of this antiserum protein in fraction No 10 was eluted after electrophoresis of extracts containing 400 mg protein per ml Protein in this

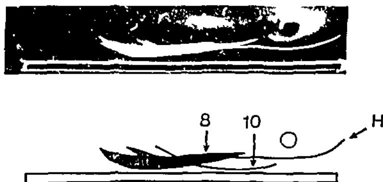


Fig 2
Photograph and drawing of immunoelectrophoresis in agarose gel of a fresh extract of bovine corneal epithelium against an antiserum obtained by immunization with electrophoretic fraction No 8 For identification of the precipitates see text

area of the gel consisted of fraction No 10 protein and some of the elec trophoretically heterogeneous protein The absorption was made with lyophyl ized protein from one volume of eluate to two volumes of antiserum. After absorption with this material the antiserum no longer precipitated with fraction 10 or fraction H The reactions of an absorbed antiserum are shown in Fig 3 This antiserum gave one precipitin line with a total extract of bovine corneal epithelium whose position corresponded to band No 8 after electrophoresis Precipitates denoted S on the drawing are apparently due to spontaneous precipitation in the gel since similar precipitates were observed when no serum was added to the antibody trough

Antisera prepared against electrophoretic fraction No 9

Fig 4 shows a typical immunoelectrophoresis with such an antiserum against a freshly prepared extract of bovine corneal epithelium containing about 60 mg protein per ml Two immunoprecipitates are seen denoted H and 10 on the schematic drawing The weak precipitate denoted 10 had a position correspond ing to electrophoretic fraction No 10 In addition there is a long precipitin line termed H which extends from the position of fractions Nos 8 to 13 Precipitates termed S are apparently due to spontaneous precipitation of a protein fraction in the gel since similar precipitates were observed in gels where no serum was filled into the antibody trough

The antiserum was absorbed with lyophylized protein prepared by elec trophoresis at pH 6 2 as described above By performing the electrophoresis at this pH antigen No 10 could be separated from the electrophoretically heterogeneous antigen and thus provide a material useful for absorption of

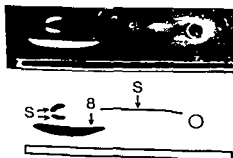


Fig 3

Photograph and drawing of immunoelectrophoresis in agarose gel of a fresh extract of bovine corneal epithelium against an antiserum absorbed to be specific against fraction No 8

against which contaminating antibodies should be removed In some cases lyophylized washed aggregated protein was used for absorption of unwanted antibodies against fraction No 9 When antisera were absorbed with proteins obtained by elution from defined segments after electrophoresis, the proteins were eluted from gels as described previously and used for absorption by mixing lyophylized protein with antiserum Controls were made by immuno electrophoresis against total extracts of bovine corneal epithelium of varying concentration to demonstrate reactivity against a single electrophoretic fraction

Experiments and Results

Antisera prepared against electrophoretic fraction No 8

A typical example of immunoelectrophoresis of a freshly prepared extract of bovine corneal epithelium with protein concentration 60 mg per ml against an unabsorbed antiserum of this kind is shown in Fig 2 Three immunoprecipitates are seen denoted 8 10 and H on the schematic drawing The points of the precipitates 8 and 10 closest to the antibody trough corresponded to the positions of bands Nos 8 and 10 after electrophoresis The immunoprecipitate denoted H covered the area from the position of fraction No 8 to fraction No 13 This extended line is typical of a reaction between antibody and the electrophoretically heterogeneous protein which has a strong tendency to precipitate spontaneously from aqueous extracts of bovine corneal epithelium

For absorption of this antiserum protein in fraction No 10 was eluted after electrophoresis of extracts containing 400 mg protein per ml Protein in this

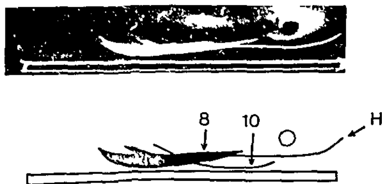


Fig 2

Photograph and drawing of immunoelectrophoresis in agarose gel of a fresh extract of bovine corneal epithelium against an antiserum obtained by immunization with electrophoretic fraction No 8 For identification of the precipitates see text

Fresh extracts of bovine corneal epithelium were incubated at 37° C for 3 hours and precipitated protein removed by ultracentrifugation Electrophoresis in agarose gel showed that protein band No 9 virtually disappeared with this procedure Immunoelectrophoresis showed that the precipitin line due to the electrophoretically heterogeneous protein antigen was shortened on the anodic side after this spontaneous precipitation of protein

Antisera prepared against electrophoretic fraction No 10

Fig 6 shows a typical finding using an unabsorbed antiserum against a freshly prepared extract containing about 60 mg protein per ml Two immunoprecipitates are seen termed Nos 10 and H on the schematic drawing The position of the precipitin arc denoted No 10 corresponded to the position of band 10 after electrophoresis The other precipitin line had an appearance typical of the electrophoretically heterogeneous antigen When the distance between the antigen well and the antibody through was increased the precipitin line cor

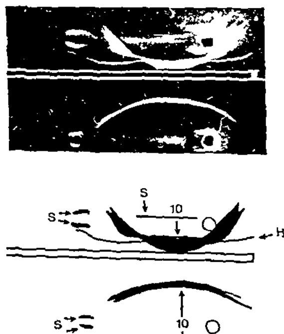


Fig 6
Photograph and drawing of immunoelectrophoresis in agarose gel of fresh extracts of bovine corneal epithelium against an unabsorbed antiserum against electrophoretic fraction No 10

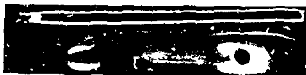




Fig 4
Photograph and drawing of immunoelectrophoresis in agarose gel of extract of bovine *corneal epithelium against an antiserum obtained by immunization with electrophoretic* fraction No 9

this type of antiserum Lyophylized protein from one volume of eluate was used for absorption of five volumes of antiserum Excess of antigen No 10 was demonstrated in the absorbed antiserum by gel diffusion tests

Fig 5 shows the findings after immunoelectrophoresis of an extract of bovine corneal epithelium using the absorbed antiserum The single precipitin line has a very characteristic position and form which proves that the antibody reacts with an electrophoretically heterogeneous antigen The "spontaneous" precipitates termed S are also seen in this instance

Antisera produced in three rabbits against protein isolated from extracts by spontaneous precipitation followed by careful washing gave similar findings The precipitin line due to the electrophoretically heterogeneous protein dominated the picture some faint additional precipitates were seen that could be absorbed by similar techniques

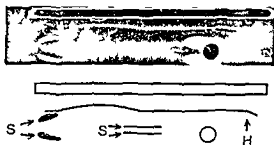


Fig 5
Similar immunoelectrophoresis using the antiserum made specific to fraction No 9 after absorption



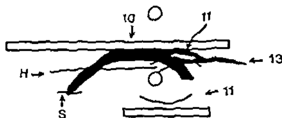


Fig 8
Photograph and drawing of immunoelectrophoresis in agarose gel of extract of bovine corneal epithelium against an antiserum against protein fraction No 11 tested without absorption and after absorption to make it specific against fraction No 11

extract of bovine corneal epithelium with protein concentration of 15 mg per ml and the antibody trough was refilled once A typical result is shown in Fig 8 where the different precipitates are denoted H 10 11 13 and S Precipitate No *11* formed double lines in all experiments with unabsorbed antiserum The peaks of the respective arcs correspond to the electrophoretic position of fractions Nos *10* 11 and *13* and the appearance of the line termed H is typical of the electrophoretically heterogeneous antigen The precipitate termed S is apparently due to spontaneous precipitation of a protein in the gel since a similar precipitate was observed in the gel when no serum was filled into the antibody trough

The antibody activity against electrophoretic fractions Nos *10* and *13* was absorbed by using lyophylized protein from equal volumes of eluates resulting from electrophoretic separation of regular extracts at pH 8 6 The antiserum was further absorbed with a sample of the electrophoretically heterogeneous antigen using twice the antiserum volume of a lyophylized eluate resulting from elution of protein from the gel after electrophoresis of concentrated extracts

Fig 8 shows the findings using the absorbed antiserum It gave a single precipitin line with the point closest to the antibody trough corresponding to the position of fraction No 11

responding to fraction No 10 became more distinct and splitting could be observed at the ends Under these conditions, no precipitate was formed between unabsorbed antiserum and the electrophoretically heterogeneous antigen

The antisera were absorbed with fraction No 9 protein eluted from gel segments after electrophoresis of concentrated extracts Lyophylized protein from two volumes of eluate was used for one volume of antiserum After such absorption, the antisera gave a single precipitin line against the total extract as shown in Fig 7 in addition to the spontaneous precipitates in the gel denoted S on the schematic drawing

Antisera prepared against electrophoretic fraction No 11

Immunoelectrophoresis was carried out in agarose gel using a freshly prepared

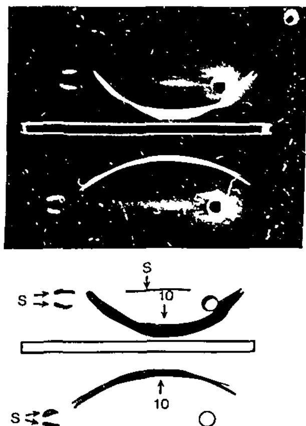


Fig 7

Similar electrophoresis as in Fig 6 using the same antiserum absorbed to specificity against fraction No 10

A search for antigenic relationship between the different components

Experiments were first made using unabsorbed anti era against fresh total extracts of bovine corneal epithelium to see which precipitin lines crossed with reactions of non identity Fig 2 illustrates that the precipitin line due to the electrophoretically heterogeneous antigen (fraction No 9) crossed the precipitin line due to fraction No 8 with an appearance typical of non identity Fig 6 shows that the precipitin line due to antigen No 9 crossed line 10 with a reaction of non identity and Fig 9 that it crossed line 13 in the same way

For electrophoretically more homogeneous antigens fewer crossings appeared in the initial immunoelectrophoretic experiments using unabsorbed antisera and total extracts The experiments were first made in this way to see how many precipitin lines would cross each other and subsequently by the double diffusion in gel technique with purified antigens In all but one experiment the precipitin lines crossed each other with reactions of non identity The exception was the precipitin line due to fraction No 8 which entered into line 10 without giving a double spur The reason for this observation is not apparent Absorption experiments indicated that fractions Nos 10 and 8 were antigenically distinct since anti 10 antisera could be absorbed with fraction 8 protein in antigen excess without significant reduction of the precipitin line between the antiserum and antigen 10 and vice versa

From the experiments it was concluded that fractions 8 9 10 11 and 13 were antigenically distinct

Discussion

The antigens of bovine corneal epithelium have previously been studied by double diffusion tests in gel and by immunoelectrophoresis using rabbit antisera produced by immunization with total extracts of the epithelium These studies were reviewed by Faure (1964) The antisera reacted with multiple components in the extracts but these were not correlated to the separation obtained by electrophoresis on paper or in agar gel The findings are also difficult to evaluate since some of the antisera were used unabsorbed so that they would also react with plasma proteins which are always present in such extracts Some proteins of bovine corneal epithelium precipitate spontaneously in agarose gel to form spurious precipitin lines (cf Fig 3) and this also complicates the evaluation François & Rabaey (1963) used antiserum absorbed with bovine serum in some experiments and up to eight precipitin lines are shown in their schematic drawings In the present investigation the four rabbits immunized with total extracts produced antibodies against various plasma proteins but precipitated with only fractions Nos 9 10 and 13 of fresh extracts Direct

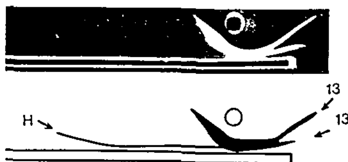


Fig 9
Immunoelectrophoresis in agarose gel of extract of proteins from bovine corneal epithelium against an antiserum against electrophoretic fraction No 13

Antisera prepared against electrophoretic fraction No 13

Immunoelectrophoresis against a total extract using unabsorbed antisera gave findings illustrated in Fig 9 A double precipitin line is seen termed 13 on the schematic drawing in addition to the extended precipitate characteristic of the electrophoretically heterogeneous antigen The antiserum was absorbed with proteins eluted from the gel after electrophoresis in the same way as antisera against fraction No 10 Fig 10 shows the findings using the absorbed antiserum after electrophoresis a double precipitate is seen The position of the point closest to the antibody well corresponded to the position of electrophoretic band No 13 since bands Nos 12 and 13 are close together it may be that the precipitate is with protein fraction No 12 rather than fraction No 13



Fig 10
Immunoelectrophoresis using the same antiserum absorbed to be specific against fraction No 13

precipitation the precipitin line due to the electrophoretically heterogeneous antigen No 9 was considerably shortened on the anodic side and there was a marked decrease of fraction No 9 after electrophoresis and staining with Amido Black B Precipitated protein was carefully washed and used for immunization The animals produced potent antisera against the electrophoretically heterogeneous antigen which appears to constitute the bulk of the spontaneously precipitated protein The reason for the marked tendency to spontaneous precipitation is not apparent This protein is a powerful antigen Subsequent experiments (Berger 1971) have shown that this antigen is tissue specific since it could not be demonstrated in extracts of other ocular components or in a variety of extracts of extra ocular origin It appears that this antigen would be particularly suitable for experiments trying to induce keratitis by immunization with a defined component of corneal tissue

Summary

Antisera were prepared by immunization of rabbits with proteins isolated by electrophoresis of freshly prepared extracts of bovine corneal epithelium in agarose gel Antisera were obtained against various protein fractions and made specific by various absorption procedures Specific antisera against electrophoretic fractions Nos 8 9 10 11 and 13 were obtained Antigen No 9 was electrophoretically heterogeneous and apparently the most potent antigen in bovine corneal epithelium in the present experiments

Acknowledgments

The author is indebted to Docent M Harboe and Dr K Hannestad for valuable advice during the work

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comparison between their and the present findings is difficult They describe a "principal fraction present in high concentration in the extracts this fraction appears to correspond to fraction No 10 in the present experiments.

When *the technique for electrophoretic separation of proteins from bovine* corneal epithelium in agarose gel was worked out the main objects were to characterise the different electrophoretic fractions obtained and to provide a method for isolation of the various proteins in amounts sufficient for preparation of specific antisera

By immunization with isolated proteins precipitating antisera of different specificities were obtained For these antisera the point of each precipitin line being closest to the antibody trough after immunoelectrophoresis was correlated with the position of the various bands after electrophoresis and staining with Amido Black It was observed that antisera against protein fractions Nos 8 10 11 and 13 gave markedly curved precipitin lines whose points closest to the antibody trough corresponded to the position of the respective bands after regular electrophoresis A slight uncertainty remained with regard to antisera against fraction No 13 since the separation of bands Nos 12 and 13 was insufficient to exclude positively that this antiserum might react with fraction No 12 instead of fraction No 13

Fraction No 9 is quite prominent after electrophoresis of freshly prepared extracts of bovine corneal epithelium This fraction diminishes markedly after spontaneous precipitation of protein from the solution during incubation at 37° C The corresponding precipitate after immunoelectrophoresis has a characteristic appearance and the antigen is electrophoretically highly heterogeneous (cf Fig 5)

No potent precipitating antisera have been obtained against fractions Nos 1–4 This is probably due to the small amount of protein in these fractions

Antigen 10 gives a thick precipitin line which splits at the ends when the antisera react with extracts of high protein concentration Further evidence of heterogeneity in this antigen has not yet been obtained Fractions Nos 11 and 13 both give two virtually parallel precipitin lines with identical electrophoretic position of the points of the precipitin lines closest to the antibody trough The observation cannot be explained at present

Antigens Nos 8 9 10 11 and 13 are probably proteins In these areas there are no bands which stain with Sudan Black B or the PAS stain Between bands Nos 11 and 13 there is a fraction which stains intensely with the PAS stain (Berger 1969) Fresh extracts were precipitated with trichloroacetic acid and the supernatants dialyzed and concentrated After electrophoresis this material gave a single band which stained intensely with the PAS stain *but did not* precipitate with anti 11 or anti 13

The aqueous extracts of bovine corneal epithelium show a marked tendency to spontaneous precipitation of protein during incubation at 37° C After such

Both drugs were instilled in the same way 2 drops and 2 minutes later *another 2 drops*

Case 1

T F A schoolboy with no relevant *heredity Always healthy* When 8 years old he first complained of blurred near vision and received glasses for constant wearing At the age of 15 the uncorrected visual acuity was 0 3 and with + 1 5 phere his vision was 1 0 bilaterally With an additional + 1 5 sphere in front of both eyes the patient read the near vision test (Jaeger No 1)

One year later the visual acuity and refraction were unchanged After full atropinization the same refractive state (+ 1 5) was found in both eyes An *additional* + *2 5 sphere* was needed bilaterally for reading The pupils were normal in size and in light and convergence reactions Eye movements and visual fields were normal The fundus of each eye including the pars plana (biomicroscopy) was fully normal as were the lens the zonule and chamber angles Somatic and neurologic examinations were normal Serologic *tests* for lues were negative Examination of the accommodation with the push up method or by inserting negative glasses in front of the eye disclosed no accommodation whatsoever

Physostigmine instilled as described above gave a refraction change of 5 D (diopters) in the right and 8 D in the left eye and for 3 % carbachol the accom modation amplitudes were 6 and 8 5 D right and left respectively

New examination at the age of 17 the same signs no voluntary accom modation

Case 2

E J A schoolgirl without relevant heredity Always healthy She was first examined at the age of 9 because of reading difficulties during the past year Her uncorrected visual acuity in each eye was 1 0 Refractive state + 0 5 sphere bilaterally With −0 5 sphere in front of the eyes the distance acuity was still 1 0 but further increase of negative spheres caused a decrease in acuity (same both eyes)

At the age of ten years the pupils were of normal size and *contracted imme* diately to light and convergence Full atropinization revealed a slight hyperopia (+ 0 5 sphere) of both eyes Lens and visible parts of zonular fibres were normal as was the fundus of each eye A somatic and neurologic examination was nor mal Serologic tests for lues were *negative She could not read small or average* sized text without glasses but with +3 5 sphere binoculary the smallest test print (Jaeger No I) was easily read

Physostigmine caused an extreme miosis (1 5 mm) but an insignificant refrac

From the Department of Ophthalmology University of Umeå
S 901 85 Umeå Sweden

PARALYSIS OF ACCOMMODATION

BY

GÖRAN TÖRNQVIST

The physiology of accommodation has for a long time been of great interest and many great ophthalmologists (Young Helmholtz Donders Hess Gullstrand) have made important contributions to our understanding of the accommodation mechanism The clinical aspects of accommodation on the other hand have aroused much less interest

The two main disorders of accommodation are spasm and paralysis the last being the most important from a neuroophthalmological point of view Paralysis of accommodation in combination with other neurological signs especially other signs of IIIrd nerve damage is seen every now and then As an isolated phenomenon such a paralysis is rare and has perhaps become more rare in the last decades because infectious diseases (diphtheria epidemic encephalitis) have become much less frequent These diseases used to be the main causes of accommodation paralysis

The following is a report of isolated paralysis of accommodation in two otherwise healthy young persons The etiological and diagnostic possibilities will be discussed

Case reports

The following drugs were used for diagnostic purposes Carbachol Isopto Karbakolin® 3% (Alcon Universal Ltd) Physostigmine (salicylate) 0 5% in aqueous solution according to Pharmacopoea Svecica(6)

Received April 20 1971

Both drugs were instilled in the same way 2 drops and 2 minutes later another 2 drops

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Physostigmine caused an extreme miosis (1 5 mm) but an insignificant refrac

tive change of only 1 D in both eyes Carbachol caused miosis (2 mm diameter) and an accommodation of 4 0 D in both eyes

Examination a year later essentially the same signs no voluntary accommodation

Discussion

Isolated bilateral and total paralysis of accommodation in two otherwise healthy young people are reported In both cases the near vision troubles seem to have developed at an age of 8 10 years (an age at which near vision demands should first manifest themselves), but the case histories are not distinct on these points The inability to accommodate has been observed for more than a year in both patients and with respect to case histories reading difficulties have been present for 8 years in case 1 and about 2 years in case 2

Carbachol (or pilocarpine) acts directly on the receptor sites of muscle cells (here ciliary muscle) Inability of carbachol to give a refractive change would thus be due to a defect in the ciliary muscle the zonule or the lens Physostigmine acts by inhibiting the destruction of acetylcholine liberated from the nerve endings

Theoretically to induce accommodation physostigmine needs a functioning neuron (post ganglionic) to the effector organ Failure of physostigmine to cause accommodation would depend on a defect in the last neuron the ciliary muscle the zonule or the lens (Of course it is also possible that a lesion of the first neuron coexists with a lesion in the second neuron) Case 1 responded to carbachol and physostigmine whereas case 2 responded to carbachol only but not to physostigmine (in spite of intense miosis) These results indicate that the paralysis of accommodation in the first case probably does not have its origin in the eye or the post ganglionic parasympathetic neuron (similar on both sides) The second case on the other hand seems to have a defect of the post ganglionic neuron

Of course the above argumentation is partly hypothetical The analysis of paralysis of accommodation by means of drugs in earlier reported cases has often be scanty and experience of drug action in cases like these is still very sparse Moreover correlation with pathologic anatomical findings are entirely lacking

In any case even if one accepts the possibility of locating the lesion pharmacologically the cause of the paralysis is still an enigma When paralysis of accommodation is associated with other symptoms both site and cause of lesion can often be discovered This is not so when paralysis is an isolated phenomenon Some commonly considered etiologies will be taken up for discussion

Ocular trauma and head trauma are unlikely in the present cases because of case histories and absence of other signs of trauma Neither of the patients had *diabetes* There was no history of *botulism* or of acute infectious diseases and serological tests for lues were negative. *Diphtheria* used to be a common cause of accommodation paralysis The present case had no history of this disease and even if abortive diphtheria can cause accommodation paralysis this type of paralysis is seldom complete and accommodation returns slowly to normal values within weeks (1 3) Where the lesion is located in diphtheria is not known Other infectious diseases often cause paralysis of accomodation for instance epidemic and perhaps also other forms of *encephalitis* These cause a nuclear paralysis which often becomes persistent If one accepts the fact that there are abortive attacks of these diseases which can give paralysis of accommodation as the only symptom encephalitis could be the etiological factor (though remote) in case one who probably has a central lesion Other possible causes of paralysis of accommodation listed in the literature (2 3 5) are irrelevant here

One case similar to the present case 1 has previously been reported Genet (4) describes a 10 year old boy otherwise healthy who developed bilateral total paralysis of accommodation There were normal responses to physostigmine (eserine) and pilocarpine This author speculates on a lesion in a hypothetical *supranuclear* accommodation centre Similar to the present case 2 five cases (7) (8) with bilateral total paralysis of accommodation in young healthy individuals where no response to physostigmine was elicited have been described Those authors believed that *congenital aplasia of the ciliary body* was the etiological factor in their cases *However both theoretically and as is evident* from the present case 2 also practically *it is quite possible that physostigmine fails to elicit any accommodation whereas directly muscle acting substances such as pilocarpine or carbachol can still give an accommodative response* The mere absence of response to physostigmine is thus not a sufficient sign for stating that aplasia of the ciliary body is present It only shows that there is a defect in the last neuron *or* the effector organ To exclude or prove a defect in the effector organ i e ciliary muscle and lens a parasympathomimetic drug such as pilocarpine or carbachol must be given

Summary

Complete bilateral paralysis of accommodation without *other* ophthalmological signs in two healthy young people is described One of *the present cases* responded with refractive change both to physostigmine and carbachol *whereas* the other case only responded to carbachol and not to physostigmine. Con

cerning the etiology of paralysis only hypotheses can be given Miotics of both types i e directly acting (acting on muscle pilocarpine, carbachol) and indirectly acting (anticholinesterase agents acting via the last neuron physostigmine) should be estimated in trying to find out the site of the lesion

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From the University Department of Ophthalmology
(Heads E Gregersen and J Edmund)
Rigshospitalet Blegdamsvej Copenhagen Denmark

ULTRASOUND OCULOMETRY AND EXOPHTHALMOMETRY IN HIGH MYOPIA WITH REFERENCE TO THE OCCURRENCE OF RETINAL DETACHMENT

BY

HANS FLEDELIUS

Earlier ultrasound studies combined with exophthalmometry have given useful information about orbital disease in uni and bilateral proptosis[1 13]

The aim of this study is to find out whether ultrasound oculometry plus exophthalmometry may show clinical importance regarding the prognosis in high myopia The high risk in this group of patients can be illustrated by the fact that numerically less than one per cent of the Danish population – i e those with high myopia – constitute about 30 per cent of Danish retinal detachment cases[5 9]

The scope of this study originates from three works in literature Bertelsen (1956)[1] reported on exophthalmometry in patients with high myopia and separated two groups according to the presence of myopic fundus lesions In the group without such lesions he found an exophthalmometric value for the myopic eye higher than that of the fellow eye while no exophthalmometric asymmetry appeared in the group with fundus changes in the myopic eye Cibis (1965)[3] suggested that disparity in growth rate of the entire eye and of the hyaloid body plays a significant role in the pathogenesis of idiopathic retinal

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cerning the etiology of paralysis, only hypotheses can be given Miotics of both types i e directly acting (acting on muscle pilocarpine carbachol) and indirectly acting (anticholinesterase agents acting via the last neuron physostigmine) should be estimated in trying to find out the site of the lesion

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Table 1

Oculometric findings in 48 patients with high myopia (unilateral in five patients bilateral in 43 patients)
Mean values – based on 88 eyes – with standard deviations (S D) in paranthesees (Eight eyes were excluded because of incomplete examination)

	Number of eyes examined	Age (years)	Corneal refractive power (Dioptr)	Exophthalmometric values (mm)	Retinoscopic refraction (Dioptr)	Ocular axial length (mm)	Depth of anterior chamber (mm)	DAC / VL (in per cent)
19 patients with retinal detachment	33	53 (range 17–78)	43 (± 1 8)	16 6 (± 2 5)	–12 7 (± 5 6)	25 92 (± 2 54)	3 6? (± 0 4)	18 1 (± 3 2)
29 patients without retinal detachment	55	45 (range 9–83)	43 (± 1 7)	16 0 (± ? 7)	–11 2 (± 5 2)	27 96 (± 2 2)	3 72 (± 0 45)	19 3 (± 3 7)
A subgroup of myopic eyes without myopic lesions from 11 of the above 48 cases	16	29			–9 4 (± 5 4)	26 96 (± 1 7)	3 84 (± 0 5)	20 9 (± 4 1)

detachment And Gernet (1965)[3] in a report on two juvenile females with bilateral tear and retinal detachment, concluded that ultrasound oculometric results might support a mechanical concept with increased tension in the uvea lens system eventually leading to retinal tears

Recent ultrasound studies have further supported the concept of some bio mechanical element in the pathogenesis of myopic fundus lesions (Curtin & Karlin 1971)[4] and retinal detachment (Grignolo et al 1969)[11] In these papers however only the axial lengths were considered and they did not deal with the eventual role of the varying dimensions of the separate eye components

The following questions may be raised Does growth of the eye anteriorly mean that the posterior eye segment is more healthy? And – may growth in the opposite orbital direction bring about retinal degenerations as a consequence of myopic stretching of the posterior segment? An answer may be found by means of exophthalmometry and oculometry

Material and Methods

48 patients with high myopia – 25 male and 23 female – were examined as follows (a) retinoscopic refraction in cycloplegia (b) keratometry (Javal Schiotz) (c) exophthalmometry (Hertel) (d) ophthalmoscopic evaluation of the fundi, and (e) time amplitude ultrasonographic measurement of depth of anterior chamber (DAC) lens thickness vitreous length (VL) and axial length

Ultrasound equipment Kretztechnik 7000 a 12 Mc Ultrasonolux transducer and a scleral contact glass filled with methocel The procedure was described in detail in a previous paper[6]

Results

The results are shown in Table I and Figs 1 and 2

The 48 patients with high myopia were divided in two groups according to the occurrence of retinal detachment (RD) which was seen in 19 patients while no detachment was present in 29 patients

Eight eyes of the total 96 could not be examined throughout and were excluded

A Exophthalmometry

The mean exophthalmometric values in the two groups showed only a minor

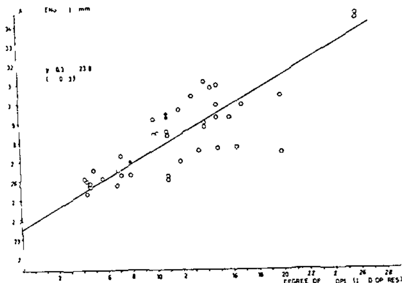


Fig 1

Correlation between degree of myopia in dioptres and axial length in mm in 88 eyes from 48 patients with high myopia Black dots = eyes from patients with retinal detachment

Conclusion Axial length and/or degree of myopia do not demonstrate any clear relation to the occurrence of retinal detachment in this material

Fig 2 shows the relation between axial lengths and the ratio anterior segment posterior segment in 88 eyes I have – as did Weekers et al [15] – chosen to express this ratio as $\frac{DAC}{VL}$ here in per cent Direct comparisons with their results however are not possible because they subtracted a mean corneal thickness (0 5 mm) from the measured DAC value

The line of regression for the whole group $y = -1\ 07\ x + 48\ 8$ reflects the well known fact that in high myopia the depth of anterior chamber – in contrast to vitreous length – increases only insignificantly with increasing axial length [10] The correlation coefficient in Fig 2 is 0 80 for the RD group alone 0 75 and 0 83 for the eyes from patients without RD The lines of regression for the two subgroups were $y = -0\ 92\ x + 44\ 6$ (for eyes in RD patients) and $y \quad -1\ 13\ x + 50\ 9$ (in the non RD group)

It would agree with the above mentioned hypothesis of Cibis[3] if the eyes of patients with retinal detachment were located predominantly below the regression line for the whole group (Fig 2) The black dots however are scattered uniformly on both sides of the line

difference (Table I), which was not statistically significant on twice the S E of Difference level

The 48 patients could be divided in three groups according to the degree of exophthalmometric asymmetry 18 patients had the same Hertel value on the two sides 16 patients had asymmetry about 1 mm and in 14 patients the asymmetry was $\geqq$ 2 mm Retinal detachment occurred evenly in the three groups (respectively in six six, and seven patients)

In fifteen cases of unilateral RD the detached retina appeared in the eye with lower Hertel value in six cases in the eye with higher Hertel value in four cases and the last five patients had symmetric Hertel values

Only five younger patients (of the 48) were without any myopic fundus lesion a further six showed myopic changes in one eye only and in these six cases no unambiguous influence of exophthalmometric values could be stated

It can be concluded that exophthalmometric values show no obvious influence on the occurrence of and degree of myopic lesion in this material which cannot confirm the observation of Bertelsen [1]

B Oculometry

Table I shows the mean values and standard deviations (S D) in the two groups Only minor differences are seen as regards corneal refraction retinoscopic refraction axial length depth of anterior chamber and the ratio $\frac{DAC}{VL}$ in per cent The differences were not statistically significant on twice the S E of Difference level

In Figs 1 and 2 the results are shown in co ordinate systems The black dots indicate single eyes from patients with RD open circles represent eyes from patients without RD

A few emmetropic and slightly hypermetropic eyes are seen they derive from patients with unilateral high myopia

The usual correlation between degree of myopia and axial length is confirmed and depicted in Fig 1 The correlation coefficient for the whole group is 0 83 and the line of regression y = 0 37 x + 23 8 In the subgroups with and without RD the correlation coefficients are 0 73 and 0 88 respectively and the regression lines y = 0 33 x + 24 5 and y = 0 39 x + 23 5 The eyes of RD patients are spread evenly on both sides of the regression line for the whole group with however a slight preponderance above the line (20 eyes above 13 below)

In 15 patients with unilateral RD eight of them showed same degree of myopia bilaterally In three cases RD occurred in the more myopic eye and in four cases in the eye with less myopia

of myopic disaster and the patients were divided in two groups according to occurrence of retinal detachment Against this it can be argued that retinal detachment is only a manifestation of severe myopic change and no major differences should be expected between such groups My intension however was to find out possible high risk factors evoking retinal detachment in high myopia

Furthermore a healthy control group was desirable consisting ideally of persons about fifty years old with myopia around –12 D without myopic fundus changes but such a group can hardly be collected Instead I have tentatively used the 16 myopic eyes without myopic lesion – in eleven of the 48 patients – as a kind of control group It differs from especially the retinal detachment group (Table I) and the $\frac{DAC}{VL}$ ratio is better but this is not significant because these eyes are shorter and less myopic Furthermore these normal patients are younger and some of them will probably with advancing age join one of the groups with myopic lesion [2,5,14]

Consequently I can only state that my oculometric search for features influencing the retinal detachment risk in high myopia has not confirmed the ideas which originated from the works of Bertelsen [1] Cibis [5] and Gernet [8] The questions raised in the introduction about the possible importance of anterior versus posterior growth of the eye are given negative answers here. It may be mentioned however that in a series not bigger than 48 patients the heterogeneity of high myopia cases forms another obstacle to unambiguous results This may be overcome in larger series allowing separation of subgroups of sufficient size for statistical analysis

Summary

A biometric study comprising keratometry retinoscopic refraction exophthalmometry and ultrasound measurement of bulbar axial length and separate eye components has been made in 48 patients with high myopia which appeared bilaterally in all but five patients 19 of the patients suffered from retinal detachment

The aim was to find out whether a relationship existed between degenerations and retinal detachments in these patients on the one hand and the anatomical proportions of the eye components on the other hand

In the present study it has not been possible to separate special high risk subgroups in high myopia according to such anatomical interrelationships

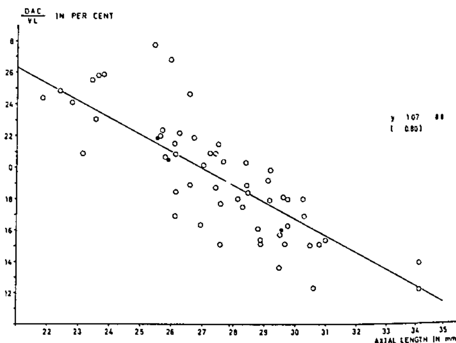


Fig 2

Correlation between axial length (in mm) and the depth of anterior chamber vitreous length $\left(\frac{DAC}{VL}\text{ in per cent}\right)$ in 88 eyes from 48 patients with high myopia Black dots = eyes from patients with retinal detachment

The $\frac{DAC}{VL}$ ratios for both eyes in patients from the RD group had the mean 18 1 per cent A mean value of 18 3 per cent could be obtained from a subgroup counting only eyes with retinal detachment the occurrence of which therefore was not confined predominantly to eyes with a $\frac{DAC}{VL}$ ratio below the mean This was supported by the fact that in the cases of unilateral RD the detached retina appeared in the eye with higher $\frac{DAC}{VL}$ value in about half of the cases

Conclusion The ratio between the sizes of anterior and posterior eye segments, here expressed as $\frac{DAC}{VL}$ in per cent showed no significant relation to the occurrence of retinal detachment in this high myopia material

Comment

As a premise in this study retinal detachment was regarded as the culmination

of myopic disaster and the patients were divided in two groups according to occurrence of retinal detachment Against this it can be argued that retinal detachment is only a manifestation of "severe myopic change" and no major differences should be expected between uch groups My intension however was to find out possible high risk factors evoking retinal detachment in high myopia

Furthermore a healthy control group was desirable consisting ideally of persons about fifty years old with myopia around −12 D without myopic fundus changes but such a group can hardly be collected Instead I have tentatively used the 16 myopic eyes without myopic lesion – in eleven of the 48 patients – as a *kind of control group* It differs from especially the retinal detachment group (Table I) and the $\frac{DAC}{VL}$ ratio is better but this is not significant because these eyes are shorter and less myopic Furthermore these normal patients are younger and some of them will probably with advancing age join one of the groups with myopic lesion [2 5 14]

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From University Eye Department Rikshospitalet Oslo Norway
(Head Professor dr med Thore Lie Thomassen)

DESCEMETOCELE AND THE LAW OF LAPLACE

BY

MARTIN DAVANGER

In a Descemetocele Descemet s membrane alone resists the intraocular pressure This is quite remarkable when taking into account that the thickness of Descemet s membrane even under normal circumstances is only 5–10 μ (Maurice 1969) The phenomenon can only be fully understood in the light of the so called *law of Laplace* which governs the relation between the pressure in a vessel and the tension in its wall

The distinction and relation between pressure and tension are often poorly understood and the words are used interchangeably In some instances as in bladder physiology this habit has greatly retarded the advance of knowledge (Burton 1960)

When applied to a spherical wall the law of Laplace may be written

$$T = \tfrac{1}{2}Pr \qquad (1)$$

where T is the tension of the wall P is the pressure in the vessel and r is the radius of curvature If P is given in gram/mm² and r in mm the designation of T will be gram/mm This measure of the tension should be understood as the load (in gram) on a 1 mm broad strip of the wall

From equation (1) is seen that at a given pressure the tension at a certain point of the wall is proportional to the radius of curvature at this point If this radius is small the tension of the wall is also relatively small If the radius of curvature is not the same at all points of a vessel the tension of the wall varies from one point to another

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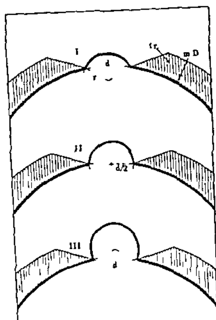


Fig 1
The 3 stages of the development of a Descemetocele Schematic

If Descemet s membrane is further distended the radius of curvature will again increase and the Descemetocele now forms more than a hemisphere (stage III Fig 1) Because the volume of the Descemetocele is very small com pared with the intraocular volume the intraocular pressure will not be reduced by this distension of the Descemetocele According to the law of Laplace the increase of the radius of curvature in this stage leads to an increase of the ten sion of the wall which in its turn leads to further distension Obviously there is now an unstable situation which will lead to perforation

It follows that when a Descemetocele approaches a complete hemisphere a perforation is imminent

The minimal tension T_D of Descemet s membrane is found in stage II when we have the minimal radius of curvature $r_{Dm\,n} = d/2$ From equation (2) follows that

$$T_{Dm} = {}^1/_2 P\, r_D = {}^1/_2 P \frac{d}{2} = \frac{1}{4} Pd \qquad (6)$$

which shows that the larger the defect of the corneal stroma the larger is the minimal tension of Descemet s membrane

As the tension of the wall of a Descemetocele is directly proportional to the intraocular pressure the distension of the Descemetocele may be reduced by lowering the intraocular pressure

It may be caulculated from the law of Laplace (when applied to a cylindrical vessel) that the tension of the wall of a capillary is only 1/1300 of the tension in the wall of vena Cava in spite of the higher pressure in a capillary Then it may be understood that the thin wall of a capillary can withstand the capillary pressure of about 30 mm Hg (Burton 1954)

According to the law of Laplace the tension T_D of Descemet s membrane in a Descemetocele is

$$T_D = {}^1/ \, Pr_D \tag{2}$$

where r_D is radius of curvature of Descemet s membrane and P is the intraocular pressure.

For comparison we consider the tension T_s of sclera i e.

$$T_s = {}^1/ \, Pr_s \tag{3}$$

where r_s is the radius of curvature of sclera

From the equations (2) and (3) follows

$$T_D = \frac{r_D}{r_s} T_s \tag{4}$$

As $r_D \ll r_s$ the tension of Descemet s membrane in a Descemetocele is much smaller than the tension of sclera r_s is normally about 12 mm and a typical value of r_D is 0 5 mm Using these values we have

$$T_D = \frac{1}{24} T_s \tag{5}$$

i e the tension of Descemet s membrane is in this case only 1/24 of the tension of sclera

In relation to the law of Laplace a Descemetocele develops through 3 stages as illustrated in Fig 1

The defect of the corneal stroma is considered circular with a diameter d In the first stage I the radius of curvature r_D is larger than d/2 and the Descemetocele is less than a hemisphere Because of the relatively large radius of curvature the tension of Descemet s membrane is relatively large But stage I is characterized by the phenomenon that *a distension of Descemet s membrane leads to a reduction of the radius of curvature which in turn leads to a reduced tension of Descemet s membrane* Therefore in stage I there is a relatively stabile balance between the forces involved

This stabile balance comes to an end in stage II in which $r_D = d/2$ (Fig 1) Now the Descemetocele forms a complete hemisphere The radius of curvature and thereby also the tension of Descemet s membrane is now as small as possible in relation to the size of the defect

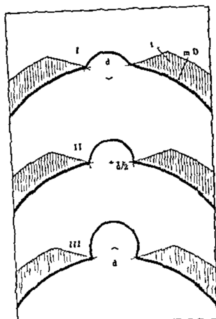


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Summary

The tension of Descemet s membrane in different stages of the development of a Descemetocele is analysed using the law of Laplace T = 1/2Pr This tension is relatively small because of the small radius of curvature of the Descemetocele It is shown that the radius of curvature, and therefore also the tension is at its minimum when the Descemetocele is semipherical A blow out" will occur if the Descemetocele develops further

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Aus der Universitats Augenklinik Halle/Saale
(Direktor Prof Dr med habil K E Kruger)

ZUM BILD DER POLYKORIE

VON

H DOMKE

Die echte Polykorie ist eine sehr seltene wenn auch meist harmlose Mißbildung die vorwiegend mit anderen Defekten am Auge kombiniert anzutreffen ist

Literaturubersichten haben *Seefelder* (*1930*) und *Badtke* (*1961*) gegeben jedoch nicht uber eigene Beobachtungen der echten Polykorie verfugt Sie stutzen sich vielmehr auf die Darstellungen von *Bergmeister* (*1919*) *Botteri* (19 0) Lapierre (1936) Carsten (1919) Giri (1918) Sedan (1927) Unger (1955 1956) Wingenroth (1899) und Lisch (1938)

Die echte Polykorie ist nach E. v Hippel (1900) charakterisiert durch das Vorhandensein zweier oder mehrerer Pupillen Jede Pupille besitzt einen den ganzen Pupillarsaum umgreifenden Sphinktermuskel und zeigt demzufolge eine Lichtreaktion und pharmakodynamische Beeinflußbarkeit Die wenigen beschriebenen Falle lassen jedoch noch keine Beurteilung uber typische Lage und Form der uberzahligen Pupillen zu

Die Sehscharfe ist bei der Polykorie oft herabgesetzt da meist Pupillarmembranreste vordere Polkatarakt oder Astigmatismus vorliegen

Wir haben Gelegenheit gehabt bei dem 18 jahrigen Hans B der wegen einer Frosio corneae des linken Auges bei uns behandelt worden ist eine Polykorie als Nebenbefund des rechten Auges zu beobachten

Eingegangen April 7 19 1



Abb 1
Haupt und Nebenpupille sind durch leuchtbar Pupille medikamentos neutral

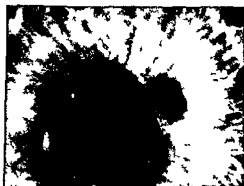


Abb 2
Partielle Mydriasis Die Nebenpupille laßt gut den Pupillarsaum erkennen

Befunde beider Augen

Sehschärfe rechts 5/10 − 0 75 sph = 5/4 Ni Text
links 5/4 Gl n angen Ni Text

Gesichtsfeldaussengren en normal Augenbinnendruck regelrecht Lider Bindehaute Hornhaute Augenvorderkammer ohne pathologischen Befund

Befund des rechten Auges

Iris blau grau atrophisch Pupille leicht vertikal oval Pupillarsaumhypoplasie zirkular aber gut vorhanden im nasalen Bereich ist der Pupillarsaum von weißlichen Faden zum Teil uberlagert direkt vom Pupillarsaum reicht ein weißlicher Faden von 5 nach 8 Uhr (uner Zugrundelegung des Uhrzifferblattes) Pupillendurchmesser ca 3 mm Bei 2 Uhr findet sich in der Pars pupillaris der Iris durch eine deutliche Brucke von der Pupille getrennt ein langliches zum Hauptpupillarsaum parallellaufendes Loch von ca 1 mm Lange mit eigenem kraftigem Pupillarsaum Im regredienten Licht sind beide Pupillen durchleuchtbar (Abb 1 und 2) und reagieren prompt auf Licht In



Abb 3
Pupille in Mydriasis Hintere Synechien und Strange tauschen unten eine weitere Nepenpupille vor



Abb 4
Pupille in Mydriasis Die obere Nebenpupille laßt den eigenen M spincter pup erkennen



Abb 5
Angedeutetes part Kolobom – eine zweite Pupille vortauschend



Abb 6
Pupille in Miosis mit persist. Pupillarmembranfaden

Mydriasis erweitert sich die Hauptpupille nur von 5 uber 9 nach 12 Uhr regelmaßig und bleibt bei 1 und 5 Uhr als hintere Synechie hangen Die Nebenpupille bei 2 Uhr erweitert sich fast kreisrund auf 2 mm Durchmesser und es ist noch ein Pigmentsaum zwischen Haupt und Nebenpupille zu erkennen. Zwischen 2 und 3 Uhr bleibt ein weißlicher gespannter Strang der eine dritte Pseudopupille vortauscht Der von 3 nach 8 Uhr beschriebene Strang ist in Mydriasis gespannt Die Linse zeigt parazentral *nach nasal umschriebene Kapseltrubungen (Abb 3 und 4) Die tieferen Augenabschnitte* sind regelrecht

Befund des linken Auges

Iris blau grau weißliche Membranreste bei 6 7 10 und 12 Uhr im Pupillarsaumgebiet und eine Pupillarsaumzyste bei 9 Uhr (unter Zugrundelegung des Uhrzifferblattes) Lichtreaktion regelrecht, in Mydriasis runde Pupille auf der Linsenvorderflache bei 3 Uhr parazentrale Pigmentauflagerungen.

Die Familiengeschichte ist unauffallig die eigene Vorgeschichte gibt keinen Hinweis fur eine abgelaufene Entzundung oder Trauma des Auges



Abb
Pupille in Mydriasis mit persist Pupillarmembranfaden.



Abb 8
Operatives Kolobom.

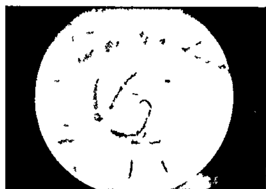


Abb 9
Kontusionell bedingte Iridodialyse



Abb 10
Hereditare Irisatrophie mit Lochbildung

Besprechung

Zur Deutung der Genese und Entwicklungsmechanik sind bisher nur spekulative Theorien aufgestellt worden Familiare Beobachtungen sind nicht bekannt Seefelder vermutet Kerbenbildungen des Augenbecherrandes die zu eigenen Pupillen answachsen konnen Badtke weist auf die Moglichkeit des unvollstandigen Verschlusses des vordersten Abschnittes der Becherspalte hin und faßt die „zweite" Pupille als partielles Kolobom auf (Abb 5)

Auffallig ist daß nicht nur in unserem Falle die Membranbildungen direkt am Pupillarsaum beginnen und zum Teil hintere Synechien" vortauschen Diese Membranbildungen stehen im Gegensatz zu der allgemein als persistierende Pupillarmembran bezeichneten Fehlbildung bei der die Fäden von der sogenannten Iriskrause ihren Ursprung nehmen (Abb 6 und 7) Diese Beobachtung unterstutzt die von Bergmeister bereits 1919 diskutierten Theorien Er hat angenommen daß diese Pupillarfäden entwicklungsgeschichtlich nicht Reste der von der Iriskrause ausgehenden Membrana pupillaris persistens sondern der Membrana capsulo pupillaris der Tunica vasculosa lentis sind Beide Membranen liegen zwar anatomisch eng beieinander sind aber in ihrer Funktion bei der Entwicklung vollig unabhangig Die Tunica vasculosa lentis mit ihrer Membrana capsulo pupillaris bildet sich gleichzeitig mit der Arteria hyaloidea im 5 bis 6 Foetalmonat zuruck Die Zuruckbildung der „eigentlichen" Pupillarmembran deren Ansatz in der Ringarterie im Bereich der spateren Iriskrause zu suchen ist erfolgt jedoch erst im 8 Foetalmonat und noch spater Daher ist zu verstehen daß die persistierende Pupillarmembran wesentlich haufiger zu beobachten ist als die persistierende Membrana capsulo pupillaris

Es wird schon wegen der Differenzen in den entwicklungsmechanischen Aufgaben verständlich daß bei der persistierenden Membrana capsulo pupillaris wesentlich häufiger Linsenanomalien als bei der persistierenden Pupil

latmembran zu finden sind Eine echte *Polykorie* wird man also nur im Bereich der Pars pupillaris der Iris zu suchen haben Sie ist kombiniert mit Resten der Membrana capsulo pupillaris Linsentrubungen persistierender Art hyaloidea Glaskorperanomalien angeborener Netzhautablösung Kammerwinkelanomalien mit Buphthalmus beobachtet worden Diese Befunde unterstutzen ebenfalls diese Annahme Angeborene Loch und Spaltbildungen der Pars ciliaris der Iris sind eher dem Kolobomkomplex einzuordnen

Foos Kiechler und Allen haben 1968 uber den ersten histologischen Befund einer Polykorie berichtet Wegen Verdachts auf Neoplasma enukleierten sie das linke Auge eines 8 Wochen alten Kindes Sie fanden eine angeborene Netzhautablosung mit Hypoplasie des Glaskorpers Kolobome der Iris des Ziliarkorpers und der Linse Polykorie Rubeosis iridis Aplasie des Sehnerven und Buphthalmus Auf Grund ihrer Befunde neigen sie zu der Ansicht von Mann, daß es sich bei der Polykorie um eine Spielart von partiellen Iriskolobomen handelt wobei Mesoderm (Sphinktermuskel) und Ektoderm gleichermaßen beteiligt sind

Die Abgrenzung der echten Polykorie von iatrogenen Irislochern z B der operativen Kolobome von Irisperforationen bei Verletzungen von kontusionell bedingten Iridodialysen oder den hereditaren Irisatrophien fallt meist nicht schwer (Abb 8 9 und 10)

Zusammenfassung

Es wird uber einen Fall der seltenen echten Polykorie berichtet bei der jede Pupille ihren eigenen vollstandigen Sphinktermuskel hat Auf die Kombination mit anderen Anomalien die Differentialdiagnose und die Entwicklungsmechanik wird hingewiesen.

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Anschrift des Verfassers
OA Dr med Heinz Domke Univ Augenklinik Halle *402 Halle/S* Leninallee 8

The Department of Ophthalmology Kommunehospitalet Copenhagen Denmark
(Heads P Brændstrup & M S Norn)

VITAL STAINING OF CORNEAL ENDOTHELIUM IN CATARACT EXTRACTION

BY

M S NORN

The corneal endothelium has a decisive influence on the course of a corneal grafting Attempts have therefore been made to evaluate the chances of survival of the endothelium by vital staining the cells (Kaufman et al Mueller Stocker et al Filkins Pakarinen Kirk et al)

If the result has been considered satisfactory i e if only weak staining has been obtained the matched donor eye has been used for the grafting The direct tested corneal graft has only been used in a few cases owing to a fear of complication due to the vital staining (Stocker et al 1970)

Is it possible to vital stain the corneal endothelium *in vivo* without running a risk of complications?

In an attempt to answer this question I have vital stained the anterior chamber during cataract extraction A total of 120 such operations were carried out with associated vital staining

The cataract extraction was carried out with cryopencil under operation microscope A limbus based conjunctival flap and two preplaced 7 0 silk sutures were employed The chamber was opened with a Beaver knife and the incision was enlarged with a pair of scissors The cornea was raised by the assistant, and the needle of a vital stain containing syringe was introduced into the lower half of the chamber after which the cornea was returned The dye solution was

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Table I
Intrabulbar vital staining a total of 99 cataract extractions

Vital stain	Number of eyes
trypan blue 0 1 %	54
trypan blue 1 %	17
mixture of 0 25 % trypan blue–0 25 % rose bengal	9
mixture of 1 % rose bengal–1 % fluorescein	19

then injected into the chamber until this was well filled The syringe was withdrawn and the cataract extraction performed

The staining of the endothelium could not be assessed till the colour produced in the chamber had faded either by washing with alpha chymotrypsin (employed in patients under 60 years of age) by loss of aqueous humour during the subsequent cataract extraction or by washing with saline in the few instances where staining was performed after the cataract extraction

During the operation the staining was assessed several times in focal light and slit lamp light through the operation microscope with and without cobalt filter

Other staining techniques have been attempted but none of these gave adequate filling of the chamber (instillation in the incision groove injection under the conjunctival flap injection into the chamber after knotting of one or more sutures)

The vital stains used were trypan blue rose bengal fluorescein and mixtures of these (Table I) The dye solutions were autoclaved at 120° for 20 minutes and supplied in glass ampoules Trypan blue stains dead cells rose bengal stains degenerate and dead cells but fluorescein penetrates into the tissue through defects of the surface (Norn 1964 1969)

Corneal Endothelium

After vital staining the corneal endothelium in most cases presented one or more transverse coloured lines These were slightly curved with downward convexity (Fig 1) The endothelium remained unstained in no more than 16 per cent

The staining was graded arbitrarily in values from 1 to 5 3 indicating

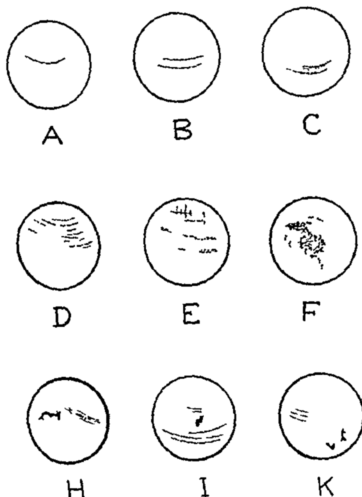


Fig 1

Vital staining of corneal endothelium in cataract extraction stained with trypan blue 0 1 A F Stained lines due to bending of the cornea F Marked endothelial damage due to corneo vitreous contact. H–K Stained lines due to cornea bending and irregular figures due to alpha chymotrypsin injection

moderate staining Table II illustrates the distribution of the staining grades in the material

The colour faded in the course of the operation. 64 per cent had lost all colour at the conclusion of the operation about 15 minutes after the vital staining had been performed Residual staining was in no case demonstrated at the first change of dressing 24 hours after the operation.

Table II

Endothelial vital staining Staining grade initially (A) and at the conclusion of the operation (B) (A) has been compared with occurrence of corneo epithelial oedema and folds of Descemet s membrane during the postoperative course The figures are per centages (*A total of 86 cataract extracted with adequately stained chamber*)

Staining grade	Number stained A	B	Corneal oedema	Folds of Descemet s membr
0	16	64	7	7
1	27	24	17	35
2	34	9	21	34
3	19	2	6	25
4	4	0	50	25

Permanent colouring (tatooing) was never noticed

The lines do not correspond in shape and position to folds of Descemet s membrane which usually cross each other, running both vertical horizontal and oblique courses In three eyes only did the lines tend to cross each other over minor areas (Fig 1 E)

The course of the lines does not correspond to that of the collagenous fibrils in the corneal parenchyma as seen in the slit lamp in polarized light nor to Fischer Schweitzer s mosaic pattern which presumably is due to properties specific of Bowman s membrane (Bron)

In one case the lens was pressed so excessively forwards during the cataract extraction that the corneal incision was left continuously half open for some length of time In this case it was plain to see that the vital stained line cor responded to the groove brought about by bending the cornea (Fig 1 C)

In the remaining cases the shape of the line likewise seemed to be account able for by bending of the cornea with groove formation on the epithelial side and similar features on the endothelial

The line is composed of innumerable dots stained blue by trypan blue and red by rose bengal A mixture of these two dyes will generally give a greenish tint with the black pupil as background With the iris or a repositor as back ground on the other hand we find red and more rarely also a few blue dots These findings suggest that the staining phenomenon is due to damage of the endothelial cells Some cells are dead (stained by trypan blue) whereas others are damaged to a smaller extent (stained by rose bengal)

In a few instances I have filled the concavity of a donor graft with trypan blue and thereafter washed with saline This gave vital stained lines owing to previous curving of the graft Histologic examination revealed trypan blue stained endothelial cells having a more intensely coloured nucleus than cyto plasm

The conclusion must accordingly be drawn that the vital stained horizontal slightly curved lines seen in relation to cataract extraction are due to damage of endothelial cells provoked by bending of the cornea on opening the chamber

Half of the alpha chymotrypsin treated eyes presented a flat oblong or irregular lesion localized so as to suggest a possible contact between needle point and *corneal endothelium* (Fig 1 H–K) Colouring *was seen particularly* in eyes with a flat chamber where it may be difficult to cautiously introduce the needle point behind the iris without transiently *just touching the cornea* No similar lesion has been demonstrated in the cases where alpha chymotrypsin had not been employed All the needles used have a rounded point

The lesion following washing with alpha chymotrypsin may be due partly to the extra manipulation required when introducing the needle into all *quadrants of the chamber* and partly *to* a direct enzymatic action on the endothelium

The linear *endothelial damages* following bending of the cornea, or the proper needle induced lesions might be conceived in some cases to cause corneal oedema or folds of Descemet's *membrane A toxic action* of the vital stained cells might possibly promote such a tendency

However no statistically significant correlation was demonstrable between the *initial or postoperative* staining grade on one hand and occurrence of corneal oedema and folds of Descemet's membrane on the other (Table II)

After staining with a mixture of rose bengal and trypan blue corneal oedema was seen in seven eyes and folds in eight *(out of nine)* suggesting a harmful effect of this mixture

The surgical technique employed is lenient and the vital staining noticed generally inconsiderable The endothelial damage was evidently in most cases too slight to provoke folds and oedema Other *factors played* a *more important* part (vitreous contact *pressure* chamber heamorhage etc)

In a case of corneal oedema and vitreous contact *after cataract extraction* the subsequent vitrectomy revealed *pronounced diffuse* endothelial staining The colour *persisted during* the whole period of operation thus demonstrating marked endothelial damage of a special kind (Fig 1 F)

In all the other cases the *cornea* was normal pre operatively as far as could be assessed by ordinary slit lamp examination

Other Sites

Chamber Injection of a vital stain into the chamber *gave in 56 patients* an impression of the spatial conditions of the chamber *during* cataract extraction.

A deep chamber showed *maximum* colouring centrally whereas if the cham

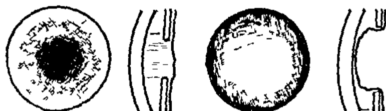


Fig 2
Trypan blue in chamber To the left a deep chamber To the right a chamber with a prominent vitreous body

ber was flat the colour was pale and even In some instances of aphakia with a prominent vitreous body, poor central staining could be seen (Fig 2)

The colour was found to decrease gradually in intensity as regenerated aqueous humour diluted the dye solution either locally in the inferior section or more diffusely By subsequent injection of alpha-chymotrypsin it was plainly seen where the enzyme was deposited the stained aqueous humour being diluted behind and at the pupillary margin

In one case after cataract extraction the anterior surface of the vitreous body was seen in the slit of the operation microscope apparently to project no further than into one third of the chamber However on subsequent vital staining we realized that the chamber was so flat as to be slit shaped and that the vitreous body practically touched the posterior corneal surface

Iris Gradually as the colour in the chamber decreased diffuse staining of the iris was seen This gradually faded leaving at the conclusion of the operation no more than spots of dye residues at the pupil or peripherally in some instances accentuated at the sites of the crypts

Lens The capsule of the cataractous lens became coloured over the area corresponding to the pupil The rest of the capsule remained unstained The colour was usually somewhat more intense with rose bengal than with trypan blue

Histologic examination of a trypan blue stained cataractous lens showed that only the capsule became stained not the cells

Vitreous body This was stained neither by trypan blue rose bengal nor fluorescein An attempt to disperse a dye drop injected into the vitreous body of an enucleated eye failed

In cataract extraction with vital stained chamber lost aqueous humour was seen to have a pale colour whereas lost vitreous was colourless

Sclera In the conjunctival incision for cataract extraction especially the epithelial border and the bottom of the wound became stained The sclera was seen to be more intensely coloured after having been damaged (e g by diathermy)

In the cases where I performed the cataract extraction through a pure corneal incision vital staining was an aid towards obtaining a correct wound adaptation Trypan blue stained the wound edges the epithelium along the edges being most intensely coloured Poor apposition of the sutures was seen as a blue double line

A small corneal wound (caused by a discission needle for instance) is best recognized by staining with trypan blue Rose bengal on the other hand often effects misleading staining all over owing to desiccation of the epithelium during the operation

Subconjunctival injection of dye close to the limbus corneae off the incisional wound resulted in prompt subconjunctival spread of the dye alond the limbus

In a few instances I have noticed that fluorescein and trypan blue may invade the chamber and stain the nearest portion of the iris presumably by penetrating through the sclera Such penetration is analogous to that of certain drugs injected subconjunctivally

Subconjunctival dye injection prior to re adjustment of prolapsed iris following cataract extraction was useful in a case where the dye appeared in the chamber and revealed a new not previously recognized wound induced diastasis

In a few cases I stained the donor graft to be used for corneal transplantation A remarkable observation made in these cases was the intensely stained endothelial lesion caused by a not quite ideal cutting of the non trephined part of the corneal disc The discs showing intense colouring of fairly large portions of the endothelium had to be discarded

Side effects

Table III gives a survey of postoperative occurrence of corneo epithelial oedema cloudy cornea and folds of Descemet s membrane in the patients subjected to intrabulbar vital staining compared with patients who had had cataract extraction done within the same period but without vital staining There was no significant difference between the two groups The figures are minimum figures

Graver complications were noticed in four cases of the vital stained series. In two of these loss of vitreous occurred during the operation (in one prior

Table III

Incidence of *postoperative corneal oedema and folds of Descemet s membrane* in vital stained and non vital stained eyes subjected to cataract extraction The figures are percentages

	Corneal oedema	Cloudy cornea	Folds of Descement s memb	No of eyes
vital stained eyes	17	6	34	99
control eyes	15	10	51	88

to vital staining) in one a psychotic patient iris prolapse was found to re quire re adjustment and in one haemochromatosis The latter was due to haemorrhage in the chamber occurring 24 hours after the operation and later repeated with a consequent secondary rise of the intra ocular pressure

In the control series there was one case of after cataract

There were altogether 14 complications in the vital stained series and 17 in the control series (fistulation non re adjustment requiring iris prolapse, tran sitorily flat chamber choroidal detachment haemorrhage and those mentioned above)

Thus vital staining with trypan blue or a mixture of rose bengal and fluorescein was found to cause no harm

However a chamber filled with 1 % trypan blue may in a few cases prevent control of the pupil and iris at the conclusion of the operation whereas no similar disadvantage has been noticed for 0 1 % trypan blue

Comments

The present investigation gave the result that trypan blue and a mixture of rose bengal and fluorescein can be used as vital stains in cataract extraction without causing any harm Similar staining can therefore perhaps be employed as an aid in evaluating a donor graft for corneal transplantation where a poor or injured endothelium is immediately detectable in the operation micro scope

Use of 0 1 % trypan blue in cataract extraction is instructive because it affords an opportunity of evaluating the frequent corneo epithelial lesions and compels one to a more gentle introduction of needle and repositor It may also aid us towards a better apposition of corneal wound edges

Summary

Vital staining of the anterior chamber during cataract extraction revealed in 84 per cent of 88 eyes one or more lines traversing the corneal endothelium

The lines are considered likely to be accountable for by damaging of endothelial cells owing to bending of the cornea during the operation

No harmful effects have been demonstrated of vital staining with 0 1 % and 1 % trypan blue or a mixture of 1 % rose bengal and 1 % fluorescein.

Vital staining is suitable for evaluating endothelial lesions (caused by the needle used for injecting alpha chymotrypsin) Further it is suitable for control of wound adaptation chamber depth and possibly also for assessing the vitality of the donor disc for corneal grafting

Acknowledgement

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From the Department of Ophthalmology
University of Goteborg S 41ɔ 4ɔ Goteborg Sweden

GENUINE RELATIVE, BINASAL HEMIANOPIA
Report of a case

BY

L. FRISÉN

Binasal hemianopia signifies bilateral lesions of non crossing visual pathway nerve fibers Tonnis (1956) observed this sign three times in a series of 3 033 intracranial tumours Binasal hemianopia is thus a very rarely encountered visual field defect It is usually associated with intracranial tumours causing an increased intracranial pressure or optochiasmatic arachnoiditis (Cushing & Walker 1912 Lutz 1928 François 1947 Staub 1952 Thierry et al 1970)

Binasal hemianopia usually starts as unequal binasal lower quadrant defects, which progress to unsymmetrical commonly irreversible hemianopias Internal isopters are less affected than peripheral ones The temporal fields are often involved as well The defect pays little if any respect to the vertical meridian Hence this is not a genuine hemianopia Binasal hemianopia thus in many ways differs from bitemporal hemianopia seen in selective interference with crossing nerve fibers This indicates not only that the non crossing nerve fiber sets no where run as exposed as the crossing ones do in the middle of the optic chiasm but also that the pathophysiological processes behind the two types of field defect are dissimilar

The following case report shows that there also exists another kind of binasal hemianopia viz a reversible relative genuinely hemianopic type Being analogous to relative bitemporal hemianopia it is considered explicable in similar terms

Received June 21 1971

Except for a mild meningitis in infancy and a proneness towards stumbling Stefania B (journal No 59 11 70) had always been in good health At the age of eleven she began to suffer from diffuse headaches Spells of nausea appeared a few months later and her general condition began to deteriorate She also began to complain of periodic dimness of vision and diplopia and she was observed to favour a tilted *position* of her head *A few weeks later she was found to* have bilateral papilledema Echo encephalography suggested internal hydrocephalus She was *then referred* from her South European home to the Department of Neurosurgery at Sahlgrenska Sjukhuset in Goteborg Sweden.

On arrival the *neurological examination* disclosed nothing abnormal besides a failing *attention* torticollis and papilledema

The neuro ophthalmological examination met with very good cooperation in spite of the patient s low age and her *impaired general* condition There were no *gross disturb*ances of the ocular *motility* Diplopia glasses uncovered a weakness of the right superior *rectus muscle* accounting for an unobtrusive torticollis The pupils were equally large and reacted normally to light including the swinging flash light The corneal sensitivity was normal

There was bilateral *papilledema* The right optic disc was hyperemic and poorly demarcated protruding one to two diopters There were several splinter hemorrhages around the disc but no white spots or signs of gliosis The veins were wide The fundus was otherwise normal The left optic disc showed similar but less *pronounced* changes the protrusion was hardly *measurable*

The visual *acuity* was 6 6 O U unaided The visual field periphery was normal to the *confrontation* test but two hand confrontation presenting one hand in each half of the monocular visual field disclosed a notably impaired *perception in the nasal half* field with a clear cut and abrupt transition *in the* vertical plane through the visual axis The perception of the *colour of* a red pen cap was similary disturbed

The visual *fields* were then examined in the Haag Streit Goldmann perimeter This examination *confirmed* the relative binasal hemianopia respecting the vertical meridian (Fig 1 open symbols) The apparently contracted periphery of the left visual field was believed to be due to fatigue this being the last *isopter explored* As was mentioned above the confrontation periphery was full and the swinging flash light test negative

The neuro ophthalmological findings were cons dered to indicate an expansive process in the chiasmal area The *following* examinations showed however that the primary lesion occupied the posterior cranial fossa

Echo encephalography indicated a low degree *dilation* of the ventricular system and a poss ble d slocation to the right There were no convinc ng localizing signs in the electroencephalogram Skull X rays disclosed an unusually large posterior fossa. There were no signs of *decalcification* in the sellar region or elsewhere Pneumo encephalography re ealed a *downward* dislocation of the cerebellar tonsils to the level of C and compres ed pontine and interpenduncular cisterns Very little gas passed into the ven tricular sy t m ne es tating ventriculography This *showed* a moderate, symmetrical d lat n of the third and lateral ventricles The aqueduct was kinked and very little gas passed nto the fourth ventricle.

W th a tentati e diagnosis *of a* verm s tumour the patient was then subjected to urge y The preparatory ventricular puncture revealed a h gh *intraventricular* pressure. Th posteri r fossa was then entered through the midline neck route and a partly cystic

From the Department of Ophthalmology
University of Göteborg S-413 45 Göteborg Sweden

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The visual *fields* were then examined in the Haag Streit *Goldmann* perimeter This *examination* confirmed the relative binasal hemi*anopia* respecting the vertical meridian (*Fig* 1 open symbols) The apparently *contracted* periphery of the left visual field was believed to be due to fatigue this being the last isopter explored As was mentioned above the confrontation *periphery* was full and the swinging flash light test negative

The neuro ophthalmological f ndings were considered to indicate an *expansive* process in the *chiasmal* area The following examinations showed however that the primary lesion occupied the poster or cran al fossa.

Echo encephalography indicated a low degree dilation of the ventricular system and a pos ible dislocation to the *right* There were no convincing *localizing signs* in the electroencephalogram Skull X rays disclosed an unusually large posterior fossa. There were no signs *of decalcification* in the sellar region *or* elsewhere Pneumo encephalography revealed a downward dislocation of the cerebellar tonsils to the level of C and compressed pontine and interpenduncular *cisterns* Very little gas passed into the ventricular system necessitating ventriculography This showed a moderate *symmetrical* d lation of the third and lateral *ventricles* The aqueduct was kinked and *very little* gas passed into th fourth ventricle.

W th a tentat ve diagnosis of a vermis tumour the patient was then subjected to s rgery Th preparatory ventricular puncture revealed a high intraventricular pressure The posteri r fossa was then entered through the midline neck route and a partly cystic

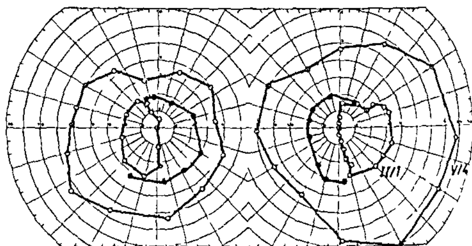


Fig 1
Perimetric findings The pre operative observations are drawn with open symbols and the postoperative central changes are inlaid with filled symbols The stimuli characteristics are indicated in the figure (Haag Streit Goldmann perimeter)

vermis tumour of mandarine size was immediately encountered The tumour a spongioblastoma was removed *in toto*

On the following night there was a respiratory arrest necessitating ventricular puncture and re exploration An extradural hematoma was evacuated Thereafter recovery was largely uneventful

The neuro ophthalmological examination was repeated two weeks later The papilledema was then slightly less prominent and the visual fields were normal to confrontation Perimetry now showed normal isopters (Fig 1 filled symbols) There was no diplopia

The papilledema decreased slowly during the following weeks The optic discs were considered normal five weeks following surgey The visual fields then showed no signs of abnormality (these latter examinations were performed by Dr Guiseppe Schisano who kindly communicated the results)

This then is a case of relative genuine binasal hemianopia in a child with internal hydrocephalus due to a giant vermis tumour Removal of the tumour restored the visual fields to normal The limited ventricular dilation and the quite moderate papilledema are noteworthy features as concerns the production of the visual field defects as will be discussed in the following

Discussion

Binasal hemianopias of the classical irregular type have been attributed to retinal diseases glaucoma retrobulbar neuritis intracranial gummata intoxica

tions arteriosclerosis hysteria etc. (Lutz 1928 Harrington 1964) Among the 52 cases with an *anatomically verified diagnosis culled from the literature by* François (1947) 17 presented optochiasmatic arachnoiditis as an acceptable explanation of their visual field defect *This will not be further discussed here* The remaining *35* cases suffered from intracranial hypertension secondary to tumour (mostly cerebellar ponto cerebellar *and* intraventricular tumours) About one half (18) of these tumours were supratentorial

The direct cause of classical binasal hemianopia *in cases of intracranial tumours is not obvious* Earlier notions that it is due to interference with the lateral parts of the optic chiasm for instance by *pressure against the internal* carotid *arteries are refuted* by the fact that non crossing nerve fibers inter mingle with crossing ones in the lateral parts of the chiasm A lateral chiasmal lesion actually *produces a homonymous* type of defect (Enoksson 1965 Hoyt 1969) Theoretically bilateral retrochiasmatic lesions might be operative but there seems to be no evidence of *such mechanisms* (Traquair 1947 Dubois Poulsen 1952) Lesions responsible for binasal hemianopia are therefore most probably related to the optic nerves

The *site* and nature of the optic nerve lesions have been discussed *for years* Naturally intracranial lesions come *to mind first. It* may then seem signif icant that *more than* one half of previously reported cases were known to display internal hydrocephalus with a distended third ventricle A ballooning third ventricle can be imagined to displace the *circulus arteriosus* and the intra cranial optic nerves so as to produce an impaired circulation *and/or mechanical* deformation irregularly interfer*ing mainly with* non crossing nerve fibers These fibers occupy the *temporal* aspects of the intracranial optic nerves Although this mechanism might be plausible in some cases *(Dubois* Poulsen 1952) it does not illuminate the pathophysiology in cases of binasal hemianopia where dis tension *of the third* ventricle was not observed Moreover a distended third ventricle may be associated with bi*temporal or* altitudinal hemianopia although the most common *finding* is normal fields (Traquair 1949 Hughes 1954 *Ruf* 1956 Huber 1961) This variability does not *disprove* a possible etiological role of a distended median ventricle *since* a variability in signs may equally well reflect the occurrence of morphological whims The *irregular absolute* type of *field* defect of classical binasal hemianopia indicates that large caliber axons serving the visual field *periphery* are more disturbed than small *caliber* ones serving *the center* of the field Such signs are *not commonly* observed in com pression of an intracranial optic nerve (Traquair 1949 Hughes 1954) *A search* for more likely loci of interference is thus appropriate. The extremely frequent association between binasal hemianopia and bilateral papilledema might be significant Although papilledema *per se* is unable to explain visual field de fects of this kind (Lutz 1928) secondary atrophy of the *optic* nerve head is well *known to* produce a seemingly equivalent *predominantly* nasal defect with a

similar natural history As the overwhelming majority of previously reported tumour cases presented bilateral papilledema mostly of long duration it appears very likely that atrophic papillary changes are causally related to the visual field defect (Cushing & Walker 1912) The view that binasal hemianopias encountered in neurosurgical practice are caused by secondary optic atrophy or chronic atrophic papilledema seems both well grounded and widely accepted (Traquair 1947 Hughes 1954 Hoyt 1969)

Whereas secondary optic atrophy may thus explain the absolute and irregular binasal field defects of a majority of cases with increased intracranial pressure this mechanism appears improbable in the present case because signs of atrophy were lacking The relative and regular binasal hemianopia observed here also obviously differs from the classical type The relative field defect seems to be explicable only as the sign of a mild and diffuse conduction defect affecting mainly small caliber axons of the two sets of non crossing nerve fibers Such a conduction disturbance is held responsible for the relative bitemporal hemianopia often encountered in chiasmatic interference with crossing fibers (Hoyt 1969)

Hughes (1954) states presumably on theoretical grounds that a *relative* binasal hemianopia indicates lateral chiasmal compression As was mentioned above lateral chiasmal compression would rather be expected to produce a homonymous type of defect Bilateral intracranial optic nerve lesions related to the distended third ventricle seem much more probable Lateral kinking of the nerves against more rigid structures lateral grooving by the internal carotids or the anterior cerebral arteries or localized circulatory impairment might be operative singly or in combination Anatomical features suggest a particularly fragile vascular supply of the temporal aspect of the intracranial optic nerve i e that part of the nerve carrying non crossing fibers (François Neetens & Colette 1958) Although clinical evidence of such a particular vulnerability seems to be lacking the lower uncrossed fibers actually often being considered the least vulnerable of all fibers this might be a case in point Of course a peculiar vascular and/or neuronal arrangement cannot be excluded in fact the operation of highly unusual factors e g optic nerve diastasis would seem likely in view of the exceptional rarity of this kind of binasal hemianopia The literature seems to mention only a few possibly equivalent cases e g the cases of binasal hemiachromatopia or hemiamblyopia reviewed by Lutz (1928) None of these had an anatomically verified diagnosis

Although the exact mechanism behind the visual field defect observed here remains open to speculation this case shows that the selective interference with the two sets of non crossing visual pathway neurons is possible and that the ensuing signs then may be analogous to those classically seen in a minimal disturbance of the crossing ones

Summary

A case of genuine relative binasal hemianopia relieved by the surgical removal of a midline *cerebellar tumour* is described The visual field findings are compatible with an intracranial mild and selective conduction disturbance of non crossing optic nerve fibers The pathogenetic mechanism therefore differs from that of classical binasal hemianopia which is usually attributed to bilateral secondary *optic atrophy*

Acknowledgement

Professor Gosta Norlen M D and Luigi Pellettieri M D at the Department of Neurosurgery kindly allowed me to have access to their records in preparing the case report

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From the Department of Ophthalmology (Heads P. Brændstrup and M. S. Norn) Kommunehospitalet, Copenhagen, Denmark

OCULAR MANIFESTATIONS IN PAGET'S DISEASE (OSTEITIS DEFORMANS)

Report of a Case with Optic Nerve Involvement and Ophthalmoplegia Responding Favourably to Adrenocorticosteroid Therapy

BY

E. BJØRN KRISTENSEN

Abstract

Paget's disease (osteitis deformans) is described with special emphasis on ophthalmological manifestations.

A case of Paget's disease with greatly impaired vision and ophthalmoplegia responded favourably to adrenocorticosteroid therapy.

Key words: Oculomotor muscles – optic nerve – osteitis deformans – Paget's disease – steroids.

Introduction

Paget's disease (osteitis deformans) with ocular manifestations is so uncommon that it was felt justified to report a case with highly impaired vision and ophthalmoplegia remitting on steroid therapy.

As is well known, Paget's disease is a chronic, progressive disease of bones

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of unknown aetiology characterized by local rarefaction followed by marked new formation of bone showing an abnormal structure The overt deforming variety is rare (2, 8 10) – about 1 16 000 – whereas radiographic studies and autopsies have revealed asymptomatic monostotic cases in 3 per cent of the population over 40 years of age with a male preponderance of 3 2 Apart from systemic symptoms and signs such as skeletal pain and deformities there may be a number of neurological signs due to narrowing of the bony foramina or impression of the base of the brain with cranial nerve palsies (deafness anosmia) headache convulsions neuralgias difficulty of speech diabetes insipidus and mental disturbances

Ocular manifestations have been classified by Ormond (7) into two groups Symptoms due to compression of nerves during their passage through narrowed bony foramina (2) Chorioretinal changes due to widespread vascular disease.

Compression of the optic nerve caused by narrowing of the optic foramen results in visual impairment and varying defects in the visual field with gradual atrophy of the optic nerve (5) An action upon the central retinal vessels must be assumed to play an important role in this development Papil oedema is observed in about one third of the cases with cranial involvement (10) either owing to an increased intracranial pressure or to local changes in the optic canal or orbit Paresis of the external ocular muscles resulting in diplopia ptosis and pain may occur as a consequence of pressure upon the nerves passing through the narrowed orbital fissure In cases of a frontal localization there may be marked degrees of exophthalmos

Chorioretinal changes are common They consist in vascular changes – corresponding to the widespread arteriosclerosis often present in these patients interfering with the blood supply to the retina and resulting in degenerative central changes with pigmented spots and punctate or streaked haemorrhages Moreover there may be choroidal haemorrhages and exudates Particular interest attaches to angioid streaks (1 6 9 10) as in such cases the prognosis is very poor because of pronounced haemorrhagic exudative macular changes with central scotomas and a highly impaired vision

The diagnosis is based upon the characteristic X ray findings (3) the greatly elevated alkaline serum phosphatase – but normal concentrations of calcium and phosphate – a highly increased urinary excretion of hydroxyproline and a moderately elevated ESR

Treatment is merely symptomatic (2 4 8) Its effect is tentatively assessed by relief from pain and normalization of the laboratory findings The most favourable agents appear to be sodium fluoride and sodium phosphate as well as adrenocorticosteroids In using the latter however some reserve is displayed owing to the unwanted side effects of the long lasting medication required

Case Report

A woman age 74 whose family history was negative especially with a view to skeletal or ocular diseases No known allergy and except for diazepam tablets 2 mg 3 times daily no medication No major illnesses except for left sided inguinal hernia treated by herniotomy

In August 1968 the patient developed without any provocation, a constant right sided frontal temporal headache occipital pain and impaired hearing in the right ear In October of the same year she consulted an ophthalmologist because of sudden diplopia and divergent strabismus in the right eye On this occasion vision in the right eye was < 6.6 but during the next 3 or 4 days vision in the right eye was entirely lost and the patient was admitted immediately At admission there was no perception of light in the right eye and vision in the left eye was 6/12 On the right there were ptosis slight protrusion and almost abolished mobility of the eyeball except for the function of the trochlear nerve which seemed intact The right pupil was larger than the left almost inactive to light but corneal sensitivity was normal So were the motility position, and surroundings of the left eye Visual field study showed left sided temporal hemimachromatopsia without macular sparing Slit lamp examination revealed diffuse conjunctival injection on both sides and incipient cataract Tension 19 mm in the right and 18 mm in the left eye The right disc was slightly faded temporally the left disc was normal but without spontaneous venous pulsation The arterioles were narrow and shiny with crossing phenomena but there were no extravasations or haemorrhages In the macular areas there were delicate displacements of pigment and minor atrophies The general condition was fairly unaffected and the blood pressure was 210 100 Bony tissue was prominent on palpation in the right frontal region. Otherwise the physical examination revealed no abnormalities Neurological examination, including EEG showed no abnormalities apart from right sided hypacusis X rays of the skull showed severe bony deformities and structural changes consisting in patchy sclerotic and osteolytic areas in the frontal bone on both sides indicating Paget's disease The other cranial bones the base of the skull and the pelvis were normal The orbital fissures and optic foramina were uninvolved and without any narrowing Right sided orbitography was also normal On the straight X ray films calcifications were visible in the internal carotid artery but right sided carotid arteriography revealed only arteriosclerosis Chest radiography showed arteriosclerotic heart disease and mild pulmonary congestion Biopsy from the right temporal artery revealed atherosclerosis The diagnosis of Paget's disease was confirmed by a highly elevated alkaline serum phosphatase of 163 U I (normally 6- 4) although the serum calcium was 9 / mg 100 ml and the serum phosphorus was 3 2 mg 100 ml i e within the normal range The ESR was moderately elevated ,6 37 mm there was mild anaemia the Hb being 10 9 g 100 ml slightly elevated alpha and beta globulin All other laboratory findings were normal

Soon after admission the vision in the left eye rapidly deteriorated to 0 5 60 in days The neurosurgeon advised against attempts at decompressing the optic nerve by operation, especially as the optic foramina showed no radiological signs of narrowing although it might be imagined that proliferative formation of connective tissue was compressing the nerves Instead steroid therapy was instituted Meticorten, 50 mg daily was administered levelled off to 15 mg in the course of 6 days. In one week the

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Figs 1 and 2
X ray of skull with sclerotic and osteolytic areas in the frontal bones and sclerotic involvement of the base of the skull including sella turcica

vision in the left eye improved to 6/36 and in another 9 days to 6/12 as compared with that on admission At the same time, the left sided visual field defects and the right sided ophthalmoplegia were normalized Vision in the right eye did not return and the right disc became atrophic The headache disappeared and the patient was feeling well on discharge. For 2 years the vision in the left eye has remained between 6/9 and 6/12 on Meticorten 7 5 mg daily Two attempts at reducing the dosage to 5 mg daily have promptly resulted in an increase in the ESR After two years follow up the status is Normal Hb ESR and serum calcium but a highly elevated alkaline serum phos phatase of 154 U/l Indeed X rays show progression of the Paget changes involving the base of the skull sella turcica and the areas adjoining the optic foramina which however still remain normal (Figs 1 and 2) The patient has been feeling well through out the follow up period

Discussion

The clinical course of headache and acute blindness might indicate temporal arteritis This fitted in with the elevation of the alpha serum globulin fraction and the negative biopsy of the temporal artery did not exclude this diagnosis However on the basis of the moderate elevation of the ESR and the other clinical radiological and laboratory findings it was felt that the phenomena were more naturally explicable as a manifestation of Paget s disease

Conclusion

Ocular signs in Paget s disease are rare To my knowledge remission of such signs on steroid therapy has not been reported previously whereas it is well known that pain may be relieved and laboratory values may return to normal If the severity of the ocular signs indicates active intervention and if neuro surgical decompression is out of the question corticosteroid medication should be tried

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I Universitätsaugenklinik Budapest
(Vorsteherin Prof M Radnót

BEITRAG ZUR FEINSTRUKTUR DER HORIZONTALZELLEN DER NETZHAUT DES HUNDES

BY

M RADNÓT

Die Herkunft und Funktion der Horizontalzellen der Netzhaut ist trotz den elektronenmikroskopischen Untersuchungen der letzten Jahre noch immer unklar Die eigenartige tubulare Struktur welche bis jetz nur in der mensch lichen Retina beschrieben wurde und den Kolmerschen Kristallen der licht mikroskopischen Bilder entspricht erweckte grosses Interesse Bis jetzt wurden diese tubularen Gebilde von Villegas Missotten Yoshida Radnot und Lovas Uga Nomura und Ikui und besonders eingehend von Dieterich untersucht und beschrieben

Im Jahre 1967 konnten wir in den Stabchen Synapsen der menschlichen Netzhaut kristallartige Einschlusse finden (Radnót und Lovas Radnot und Mitarb) Diese Befunde werden von Uga Nomura und Ikui sowie von Dieterich und Rohen bestatigt In weiteren Untersuchungen konnten wir fest stellen dass man nach intensiver Belichtung sehr viel kristallartige Gebilde findet (Radnót und Mitarb) Die Befunde von Yamada und Okuda waren uns unbekannt und sind uns auch jetzt nur als Zitate in der Arbeit von Uga und Ikui zugänglich

Hebel fand die kristallartigen Korperchen in den Synapsen des Hundeauges Auf Grund der Lokalisation der Kristallkorperchen vermuteten wir dass sie in der Triade immer in dem Fortsatz der Horizontalzelle zu finden sind aber wir

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1a
1b

konnten bisher in keinem Falle den Fortsatz bis zur Horizontalzelle verfolgen Auch dachten wir daran dass zwischen den Kristallen und den tubularen Strukturen ein Zusammenhang sein könnte Diese Annahme veranlasste uns Belichtungsexperimente bei Hunden vorzunehmen und nach den obigen beiden Strukturen zu fahnden

Material und Methodik

Bei funf Hunden (4 Bastarde und ein Wolfshund) haben wir Belichtung eines Auges vorgenommen das andere Auge diente als Kontrolle Die Belichtung dauerte in vier Fallen 45 in einem Falle 20 lang Die Lichtquelle wurde 50 cm vor dem Auge angewandt die Lichtstarke betrug 80 000 Lux Nach Enucleation wurde die Netzhaut z T in Glutaraldehyd z T in Osmium fixiert In keinem Fall wurde perfundiert Die Netzhautstuckchen wurden in Araldit eingebettet mit Reichert Ultramikrotom geschnitten und mit Jem 7 A Elektronenmikroskop untersucht und photographiert

Befunde

In den Horizontalzellen der ausseren Kornerschicht finden wir einen rundlichen Kern in welchem das Karyoplasma zerstreut dunklere und hellere Partikel aufweist Im Cytoplasma ist das Golgi Apparat z T neben dem Kern aber in gewissen Fallen erstreckt sich das Golgi Feld bis zur Cytomembran Im Golgi Feld sind zahlreiche Vesikel (oder Querschnitte der Tubuli?) zu sehen Die meisten sind optisch leer oder weisen eine sehr minimale Elektrodensitat auf Die Vesikel sind in grosser Zahl vorhanden und sind von verschiedener Grosse Auch perlschnurartige Blaschenreihen sind zu sehen An einigen Vesikel haften Ribosomen bzw Ribosomenaggregate Die Vesikel sind an vielen Stellen ringartig d h sie bilden eine ringartige Zone welche eine leichte Elektrodensitat aufweist die Mitte scheint leer zu sein An diesem Ring haften Ribosomen bzw Ribosomenkomplexe (Abb 1) Diese Vesikel sind meistens rund um das Golgi Apparat angeordnet An vielen Stellen haften die Ribosomen dicht nebeneinander an den Vesikeln und so entstehen Bilder (Abb 1a) welche den Querschnitten der oben erwahnten tubularen Strukturen der Horizontalzellen des Menschen nicht nur ahneln sondern mit denen identisch zu sein scheinen

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Abb 1

Horizontalzelle G = Golgi Komplex R = Ribosomen T Tubulare Structuren

Abb 1a Querschnitt der tubularen Strukturen

Abb 1b Langschnitt einer tubularen Struktur

Dass es sich um tubuläre Strukture handelt zeigt Abb 1b und 2b Dass die an diesen Vesikeln oder Rohren haftende Partikel Ribosomen sind zeigen diese Bilder eindeutig Ribosomen sind verstreut im Zytoplasma zu finden u zw bilden sie meist Komplexe An vielen Stellen sind sie in Reihen geordnet bilden kleinere grössere Rosetten und andere Ribosomengruppen (Abb 2b) Allerdings *haben wir bisher nie mehr als drei Tubuli bzw deren Querschnitte in einer* Gruppe gefunden

Wir finden in den *Horizontalzellen auch Mitochondrien* deren Cristae z T gut erhalten sind (Abb 1)

In der äusseren Faserschicht findet man in den Stäbchensynapsen kristall artige Gebilde welche genau so gestaltet sind wie wir sie bei der menschlichen Hornhaut beschrieben haben Synaptische Bläschen sind sowohl auf der prae - wie auf der postsynaptischen Seite vorhanden Auch grossere Bläschen sind zu finden Die synaptische Lamelle umgeben von synaptischen Vesikeln ist auch auf Abb 2 gut zu beobachten Auch in diesem Falle war es unmoglich den invaginierten Fortsatz welcher den Kristalleinschluss beherbergt bis zur Zelle *zu verfolgen* Aber die Randstellung weist darauf hin *dass es sich* wahr scheinlich um eine Horizontalzelle handelt

Besprechung

Wir haben in Hundenetzhäuten in den Horizontalzellen ähnliche Organellen gefunden wie sie Dieterich in den menschlichen Horizontalzellen beschreibt

Wir stimmen mit ihm darin überein dass die Blaschen vom Golgi Apparat stammen Wir haben Gebilde gefunden welche grosse Ahnlichkeit mit den tubularen Strukturen der menschlichen Horizontalzellen aufweisen und glauben dass diese von den abgeschnurten Vesikeln des Golgi Apparates dadurch ent stehen dass auf ihnen Ribosomen und Ribosomen komplexe haften Im Zell plasma sind Ribosomenkomplexe in Ketten in verschiedenen Gruppen und in kleineren *grösseren Rosetten angeordnet zu sehen*

Die Grosse und Anordung der Aggregate zeigt – wie das schon auch bisher von Missotten Radnot und Lovas Uga und Ikui sowie Uga und Mitarb und Dieterich angenommen wurde – dass es sich um Ribosomen bzw Ribosomen aggregate handelt

Die Kristallkorper der Synapsen wenn sie tatsachlich von den Fortsatzen der Horizontalzellen beherbergt werden waren deshalb von besonderer Be deutung da in Zellen welche reich an Ribosomen sind *kristallische* Ribosom

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Abb 2

Stabchensynapse K = Kristallkorper L = Synaptische Lamelle V = Synaptische Vesikel

Abb 2b Horizontalzelle T – Tubulare Struktur R – Ribosomen C = Vesikeln

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aggregate entstehen Neuerdings konnten Barbieri und Mitarb durch ihre neue Methode kristallische und nicht kristallische Ribosomaggregate in vitro isolieren Die Grösse die Form und Anordnung der Aggregate weist grosse Ähnlichkeit mit unseren Befunden auf Ob es sich bei den Kristalleinschlussen um Ribosomenkristalle handelt muss aber noch durch enzymatische Untersuchungen bestätigt werden

Wir möchten noch daran erinnern dass ähnliche kristallartige Gebilde nicht nur in den Photorezeptorsynapsen sondern in verschiedenen Zellen des Augen gefunden wurden so in den Gefässendothelzellen der Netzhaut (Ishikawa Bloodworth und Molitor) in den Gefässendothelien des Ciliarkörpers (Fine) in der Choriocapillaris (Radnot und Lovas) sowie in Endothelien in den Basalzellen des Epithels und in Fibozyten der Bindehaut des Hundes (Radnot und Trux) Die Kristallstrukturen dieser Einschlüsse sind einander sehr ahnlich Es muss sich also um eine Substanz welche in verschiedenen Zellen vorkommt, handeln Allerdings wiesen alle Zellen in welchen die Einschlusse gefunden wurden hohen Ribosomengehalt auf

Dieterich und Rohen wiesen darauf hin dass zwischen der Netzhaut des Menschen und des Rhesusaffen grössere strukturelle Differenzen bestehen und dass man die Befunde an Affen nicht immer auf Menschen beziehen kann

Auf Grund der bisherigen Untersuchungen an Hundenetzhäuten glauben wir dass vielleicht diese Netzhäute in gewisser Hinsicht der menschlichen Netzhaut verwandter sind Allerdings steht fest dass Kristalle der Stäbchensynapsen bischer in der Rhesusnetzhaut nicht gefunden wurden Die Anordung der Kristallkörperchen die in den Rhesusnetzhäuten neben den Zapfensynapsen gefunden wurden konnten in der menschlichen Netzhaut bisher nicht bewiesen werden Die Kristalleinschlüsse die von Hebel beim Hund beschrieben wurden und die wir auch gefunden haben sind den Befunden der menschlichen Netzhaut sehr ähnlich

Zusammenfassung

Bei der Untersuchung von funf Hundenetzhäuten konnte festgestellt werden dass in den Horizontalzellen des Hundes ahnliche tubulare Gebilde vorkommen wie sie in der menschlichen Retina bekannt sind Die tubularen bzw vesikulären Strukturen an welchen Ribosomen haften stammen vom Golgi Apparat Im Cytoplasma der Horizontalzellen sind Ribosomenaggregate in grosser Menge vorhanden In den Stabchensynapsen waren den Befunden der menschlichen Netzhaut ahnliche kristallartige Einschlüsse zu finden

It might be interesting *to discuss the dimensions of the schematic eye* using some of the new data which have been published since 1909

One of the problems is the dioptric power of the lens and the positions of its principal points The curvatures and positions of the surfaces of the lens are known with reasonable precision (Nordenson 1913) The substance of the lens however consists of a medium of variable index of refraction the index is lower in the superficial parts of the lens higher in the core In youth the variation of the index is continuous throughout the lens later light reflexes begin to be visible implying a discontinuity in the variation of the index of refraction This makes it impossible to obtain the optical data of the lens directly from the curvatures of its surfaces and the indices of refraction The data of the lens are *found from the refraction of aphakic eyes or by calculation from the dioptric* power of the cornea and the length of the axis of the eye Those data are however insufficient to find both the dioptric power of the lens and the position of its principal points

The relations between the position of the *first principal point of the lens and the total* dioptric power of the eye

Table of symbols

Dioptric power of the cornea C – dioptric power of the lens L – dioptric power of the eye as a whole D

Length of axis of the eye from the second principal point of the cornea to the fovea b

Distance from the second principal point of the cornea to the first principal point of the lens d

Index of refraction of the aqueous and the vitreous n

Radius of the cornea r

Using Gullstrand s formulae (*loc cit* p 283) for a combination of two optical systems it is found

$$D = C + L - \frac{d}{n}CL \tag{1}$$

and the distance of the second principal point of the eye is

$$-\frac{d\ C}{nD} \text{ from the first principal point of the lens} \tag{2}$$

From the Eye Clinic
Malmo Allmanna Sjukhus University of Lund
(Head Professor Gote Osterlind)

THE POSITION OF THE FIRST PRINCIPAL POINT OF THE LENS IN A SCHEMATIC EYE

BY

ULF HALLDÉN

Summary

The dimensions of the schematic eye are discussed using recent data on the curvature of the anterior surface of the cornea and the length of the axis of the eye The aniseiconia caused by correction of unilateral aphakia by contact lenses is used to find the position of the first principal point of the lens the total dioptric power of the eye and the dioptric power of the lens

Key words schematic eye principal points size of retinal image aniseiconia

Introduction

A schematic eye is a theoretical model whose optical properties and dimensions correspond to those of the average living eye Such a model is useful for visualizing the optical properties of the eye for optical calculations and in the study of physiological optics The latest schematic eye was calculated by Gullstrand (1909) and published in the third edition of *Helmholtz Physiological Optics* Since then progress has been made in the methods of investigation most important the method for measuring the length of the axis of the living eye which was introduced by Rushton (1938)

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Using Gullstrand s formulae (loc cit p 283) for a combination of two optical systems it is found

$$D = C + L - \frac{d}{n} CL \tag{1}$$

and the distance of the second principal point of the eye is

$$-\frac{d}{n}\frac{C}{D} \text{ from the } \textit{first principal} \text{ point of the lens} \tag{2}$$

The dioptric power of an emmetropic eye is equal to the reciprocal of the reduced distance from second principal point of the eye to the fovea

$$D = \frac{1}{\frac{b}{n} - \left(\frac{d}{n} - \frac{d}{nD}C\right)}$$

which can be simplified to

$$D = \frac{1 - \frac{d}{n} C}{\frac{b}{n} - \frac{d}{n}} \quad (3)$$

Equation (1) gives the dioptric power of the lens

$$L = \frac{D - C}{1 - \frac{d}{n} C} \quad (4)$$

Equations (3) and (4) show that an error in the position of the first principal point will give a corresponding error in the dioptric power of the lens and in the total dioptric power of the eye

To find the numerical values of the relations between d D and L it is necessary to have reliable figures for C b and n

Stenström (1946) has measured the refraction the radius of the cornea and the length of the internal axis of the eye in 1000 eyes and we will use the mean values given by him The mean value of the refraction was + 0 12 but as the measurements of the refraction were made at 10 m corresponding to 0 10 dioptr the refraction can be regarded as almost exactly emmetropic The radius of the cornea was 7 86 mm and the length of the internal axis of the eye was 24 00 mm

Using the traditional values for the radius of the posterior surface of the cornea 6 80 mm the thickness of the cornea 0 50 mm for the index of refraction of the corneal substance 1 376 and for the index of refraction of the aqueous 1 336 it is found that the dioptric power of the corneal surfaces are +47 837 and –5 882 The dioptric power of the cornea system is 42 057 and the position of both the principal points of the system is 0 05 mm in front of the anterior surface of the cornea

For the value of b should be chosen the distance from the second principal point of the cornea system to the fovea i e 24 05 mm

If C is 42 057 and b 24 05 the relations between D d and L as found by eq (3) and (4) are shown in the diagram

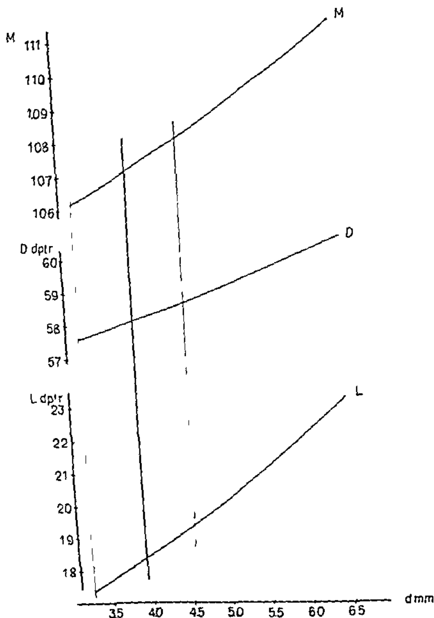


Fig. 1

The d agram sh ws the relation between the distance from the second principal point of the co nea to the first principal point of the lens (d) the d optric power of the lens (L) the total dioptric power of the optical system of the eye (D) and the mag n fi ati n f the retinal image caused by substituting the crystalline lens by a corneal c ntact len specified n the text (M)

The heavy ert cal line shows the values of the modified schematic eye the fine v rtical lines the limits of twice the standard error of the mean value.

The dioptric power of an emmetropic eye is equal to the reciprocal of the reduced distance from second principal point of the eye to the fovea

$$D = \frac{1}{\frac{b}{n} - \left(\frac{d}{n} - \frac{d\ C}{nD}\right)}$$

which can be simplified to

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If C is 42 057 and b 24 05 the relations between D d and L as found by eq (3) and (4) are shown in the diagram

We now find from the aniseiconia of 7 09 per cent that the total dioptric power of the schematic eye is

$$D = 1\ 0709 \quad 54\ 295 = 58\ 145$$

The corresponding values are $L = 18\ 364$ and $d = 3\ 94$ mm

From those values it is possible to calculate the positions of the principal points of the optical system of the whole eye. The reduced distances are from the second principal point of the cornea to the first principal point of the whole eye 0 93 mm and from the first principal point of the lens to the second principal point of the whole eye -2 13 mm.

Now the fundamental constants are known and the complete data can be collected in a table

Table of schematic eye

Index of refraction of cornea	1 376
Index of refraction of aqueous	1 336
Position of anterior surface of cornea	0
Position of posterior surface of cornea	0.50
Radius of anterior surface of cornea	7 86 mm
Radius of posterior surface of cornea	6 80 mm
Dioptric power of anterior surface of cornea	47 84
Dioptric power of posterior surface of cornea	– 5 88
Cornea system	
Dioptric power	42 06
Positions of first and second principal points	– 0 05 mm
Lens system	
Dioptric power	18 36
Position of first principal point	3 89 mm
Complete system of eye	
Dioptric power	58 15
Position of first principal point	0 88 mm
Position of second principal point	1 04 mm
Position of first focal point	–16 32 mm
Position of second focal point	24 02 mm
First focal length	17 20 mm
Second focal length	22 98 mm
Position of retinal fovea	24 00 mm
Hypermetropia along axis	0 04 dptr

If a reliable value of the total dioptric power of the optical system is found it is possible to read the values of d and L from the diagram

The size of the retinal image

The size of the retinal image is proportional to the reciprocal of the total dioptric power of the eye Direct measurement by X rays, of the retinal image of the eye has been made by Goldmann & Hagen (1942) They measured D in 18 eyes, 10 emmetropic 1 hyperopic, and 7 myopic The mean value of D in the emmetropic eyes was 59 50, which gives values of L = 21 19 and d = 5 5 mm In Goldmann & Hagen s investigations the retinal image was large corresponding to a visual angle of about 19° This is an important source of error because of distortion The type of distortion present in the human eye is probably barrel distortion the magnification of the image is not uniform but decreases with the distance from the optical axis This will give higher value of D if the retinal image is large consequently the value D = 59 50 is probably too high

Another way to find the total dioptric power of the eye is to study the aniseiconia caused by unilateral aphakia

In a number of cases unilateral aphakia has been corrected by corneal contact lenses Constantine & McLean (1954) have given values of the aniseiconia in 7 cases and Girard et al (1962) in 28 cases The mean value of the aniseiconia in those 35 cases was 7 09 per cent the standard deviation was ± 2 32 and the standard error of the mean was ± 0 39

If an aphakia is corrected with a contact lens the position of the second principal point of the contact lens cornea system will differ from that of the unaided cornea In fact the difference will be small but it seems to be useful to calculate the dioptric power and the position of the second principal point of the contact lens cornea system The data of the contact lenses used by the authors quoted are not given and it will be necessary to make the calculations from a schematic contact lens The following data of the contact lens are assumed index of refraction 1 496 thickness 0 40 mm radius of posterior surface 7 86 mm (equal to that of the cornea) Assuming that the tear film between the lens and the cornea is extremely thin the dioptric power of the posterior surface of the lens is –15 267 The anterior surface of the cornea is now eliminated The posterior surface of the cornea has a dioptric power of–5 882 By successive application of the formulae for the combination of two optical system given by Gullstrand (loc cit p 283) it can be shown that the aphakic schematic eye is corrected if the radius of the anterior surface of the contact lens is 6 65 mm The reduced distance from the anterior surface of the cornea to the second principal point of the contact lens cornea system is –0 465 mm and the dioptric power of the system is 54 295

We now find from the aniseiconia of 7 09 per cent that the total dioptric power of the schematic eye is

$$D = 1\ 0709 \quad 54\ 295 = 58\ 145$$

The corresponding values are L = 18 364 and d = 3 94 mm

From those values it is possible to calculate the positions of the principal points of the optical system of the whole eye The reduced distances are from the second principal point of the cornea to the first principal point of the whole eye 0 93 mm and from the first principal point of the lens to the second principal point of the whole eye -2 13 mm

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Table of schematic eye

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Position of first principal point	0 88 mm
Position of second principal point	1 04 mm
Position of first focal point	–16 32 mm
Position of second focal point	24 02 mm
First focal length	17 20 mm
Second focal length	22 98 mm
Position of retinal fovea	24 00 mm
Hypermetropia along axis	0 04 dptr

The schematic eye was intended to be emmetropic The difference 0 02 mm between the positions of the second focal point and the retina and the hyper metropia of 0 04 dptr are the results of the approximations performed

Discussion

A comparison between the schematic eye of Gullstrand and this modified sche matic eye shows that the fundamental difference is the position of the first principal point of the lens

Gullstrand (loc cit) calculated the positions of the principal points from a schematic lens Most of the data of this lens were based on measurements the positions and radii of curvature of the two surfaces of the lens the indices of refraction of the cortex and the centre of the lens The dioctric power of the core of the lens was calculated from the loss of refracting power of the eye after the extraction of cataract

A number of data however had to be assumed that the curvatures of adja cent isoindicial surfaces were equal the position of the centre" of the lens that one of the constants of Matthiesen s indicial equation was equal to zero The result of those assumptions was that the positions of the principal points of the core lens and consequently the radii of curvature and the positions of the re fracting surfaces of the equivalent core lens were uncertain The magnitude of this uncertainty is difficult to estimate

In the modified schematic eye the position of the first principal point of the lens was calculated from the magnification of the retinal image caused by substituting the crystalline lens by a corneal contact lens Here the standard error of the mean value of the aniseiconia might be used as a measure of the uncertainty It is true that the original refraction of the eyes studied by the authors quoted is unknown and certainly not always emmetropic This could be expected to give a value of the standard error of the mean which is too high The difference is however probably small as the correlation between the re fraction and the total dioptric power of the eye is known to be small (Stenström 1946) The standard error of the mean of the aniseiconia was 0 39 per cent If the limits chosen are twice *the standard error of the mean the maximum* value of the magnification is 1 0807 and the minimum 1 0612 The corresponding values of d are 4 6 and 3 3 mm of D 58 68 and 57 62 and of L 19 43 and 17 34 as shown by the fine vertical lines of the diagram

The distance from the anterior surface of the cornea to the first principal point of the lens in Gullstrand s schematic eye is 5 678 mm If the crystalline lens is substituted by a corneal contact lens this figure would give a magnifi cation of the retinal image of more than 1 09 which value does not agree with the observations

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From the Eye Clinic
Malmö Allmänna Sjukhus University of Lund Sweden
(Head Professor Gote Osterlind)

OPTICAL ASYMMETRIES OF THE EYE AND THE ASYMMETRY OF THE HORIZONTAL SUBJECTIVE METRIC

BY

ULF HALLDÉN

Our visual impressions arrange themselves to coherent pictures and the relative position of objects in space is perceived because each retinal element has a certain spatial value or local sign When a retinal element is stimulated, it gives rise to a sensation that the object from which the light rays come has a definite location in space The fovea has the spatial value of the straight ahead position All retinal points on the nasal side of the fovea have local signs of the temporal visual field and all retinal points on the temporal side of the fovea have local signs of the nasal part of the field of vision This is the concept of functional local signs which is fundamental to the study of the perception of space

The question whether the local signs of retinal points are determined by genetic endowment or whether they are acquired by learning has been the subject of much discussion The problem is not devoid of practical interest Anomalous correspondence which is common in concomitant strabismus seems to be caused by a kind of learning The problem might even cast some light on wider questions of the relation between genetic endowment and learning in the central nervous system

This is the reason why minor discrepancies in the spatial values of retinal points have been the subject of much investigation The most interesting of those discrepancies is that of the horizontal subjective metric In monocular

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vision this is studied by the well known bisectioning experiment of Kundt (1863) A monocular asymmetry is measured by asking the subject to bisect a given horizontal line subjectively while keeping the fixation steadfast on the midpoint Usually it is found that the temporal segment of the line is longer than the nasal one (Kundt asymmetry) but the reverse asymmetry (Munsterberg) is found in some eyes

In binocular vision the Kundt asymmetry results in the Hering Hillebrand horopterdeviation The connection between the Kundt asymmetry and the horopterdeviation was already known to Hillebrand (1893) and has been illustrated by the experiments of Frank (1905) Fischer (1924) Herzau (1929) and Ogle (1950)

The Kundt asymmetry can be explained in two ways It might be caused by an asymmetrical distribution of the spatial values of retinal points or by an asymmetry of the optical system of the eye The first hypothesis was proposed by Hillebrand and is at present accepted by most investigators The second one is the object of the present investigation

Of optical asymmetries of the eye one is well known and easily measured This is the angle between the normal to the cornea that goes through the centre of the pupil and the line of sight of the eye the Visierlinie of Helmholtz This angle has been called by different authors α γ and $\varkappa$ I believe that γ first used by Mayerhausen (1882) should be regarded as the correct symbol for reasons of historical priority The angle α of Helmholtz is not identical with γ but has approximately the same value It has been shown that the angle γ will cause a small degree of inverse astigmatism (Gullstrand 1891 Tscherning 1892 Berg 1939) The angle γ however does not in itself explain the Kundt asymmetry Little is known about other asymmetries of the optical system of the eye

One optical asymmetry which might be important is the angle between the visual axis of the eye and the geometrical axis of the retina We will call this angle δ I have discussed this asymmetry and its importance for the Hering Hillebrand horopterdeviation in an earlier communication (Hallden 1956) Direct measurements of angle δ do not seem practicable

It is possible that there exists a common normal to the two surfaces of the lens which might be called the optical axis of the lens The optical axis of the lens does not usually coincide with the optical axis of the cornea Tscherning (1892) observed this when investigating the optical axis of the lens in 10 eyes Nordenson (1913) had to examine 22 eyes before he found 3 eyes sufficiently well centered to allow his measurements of the curvatures of the surfaces of the lens of the human eye The angle between the optical axis of the cornea and the optical axis of the lens will in the following be called the angle ε Measurements of the optical axis of the lens seem to be difficult and the data necessary to calculate the angle ε are not available The angle ε will cause an asymmetry of magnification

There are consequently, at least two optical asymmetries of the eye, each of which could give an adequate explanation of the bisectioning experiment of Kundt and of the Hering Hillebrand horopterdeviation Those optical asymmetries are difficult or impossible to measure directly It is however probable that they co variate with the angle γ which is easy to measure A study of the co variation between the angle γ and bisectioning experiment of Kundt consequently seems to be of some interest

Measurement of the angle γ

The measurements of the angle γ were performed according to the method described by Gullstrand (1891) The apparatus consisted of a headrest a telescope a transparent celluloid scale and an ophthalmoscope which served as a source of light A fixation mark for the subject was glued to the centre of the front surface of the objective lens of the telescope The distance from the vertex of the cornea of the subject to the celluloid scale was fixed at 670 mm The ophthalmoscope was moved along the celluloid scale until the corneal reflex was seen in the centre of the pupil of the subject The distance measured in this way is proportional to the tangent of the double angle between the normal to the cornea that goes through the centre of the pupil and the line of sight that is to $tg\ 2\gamma$

This measurement is easy to perform and seems to be rather precise There is however one source of error which merits discussion When the observer decides that he sees the corneal reflex in the centre of the pupil of the subject s eye he performs a bisectioning measurement affected with a Kundt error If the absolute value of γ is important this error can be avoided by using an ophthalmometer instead of the telescope or it can be corrected for by measuring the Kundt error of the observer For this investigation however the interest is concentrated not on the absolute values but on the variations of the angle γ All measurements of γ were performed by the same observer using the right eye and on the right eyes of the subjects In this way the individual variations of the angle are correctly measured even if the absolute values of the angle are affected with a slight systematic error

Measurement of the Kundt asymmetry

There are no standard units or standard methods of measurement for the study of the horizontal subjective metric For the present purpose the unit K will be used defined by

$$K = 1000 \frac{t - n}{a}$$

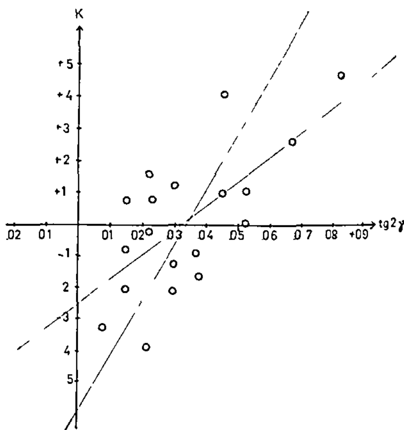
where t and n are respectively the temporal and the nasal parts of the line bisectioned and a is the distance from the midpoint of the line to the eye. A positive value of K means that the temporal part of the line is larger than the nasal one a Kundt type error a negative value means an error of the Munsterberg type

It is not known whether there is a linear relationship between K and the visual angle of the line $\frac{t+n}{a}$ and it is quite possible that the monocular asymmetries are more complicated or even irregular For this reason all bisectioning experiments were performed on identical straight horizontal lines 31 mm long and at the same distance 400 mm

Each subject performed about 20 such bisectioning experiments Afterwards the temporal and nasal parts of each line were measured with vernier callipers and the difference calculated For each subject the mean value of K the stand

Table

Subject	tg 2 γ	Number of measurements of K	Mean value of K	Standard error of mean value of K
A	0 052	[illegible]0	1 03	0 30
B	0 067	[illegible]8	[illegible] 60	0 28
C	0 02[illegible]	20	-0 [illegible]	0 30
D	0 045	[illegible]8	4 08	0 40
E	0 022	[illegible]8	-3 90	0 53
F	0 01[illegible]	[illegible]5	-2 03	0 28
G	0 052	25	0 0[illegible]	0.35
H	0 08[illegible]	29	4 65	0.33
I	0 037	27	-0 90	0 30
J	0 04[illegible]	[illegible]8	1 00	0 45
K	0 0[illegible]	[illegible]0	1 60	0 15
L	0 008	19	-3 25	0.33
M	0 038	15	-1 63	0 4[illegible]
N	0 030	21	1 [illegible]0	0.30
O	0 050	[illegible]0	-2 10	0.23
P	0 015	21	-0 08	0 [illegible]
Q	0 030	15	-1.23	0.33
R	0 015	[illegible]0	0 60	0.35
S	0 0[illegible]3	17	0 80	0 28



Diagram

Each ring gives the value of 2 γ and K for one of the subjects The two fine lines on the diagram are the lines of regression calculated from the data in the table

ard deviation of K and the standard error of the mean value of K $\frac{\sigma}{\sqrt{n-1}}$ were calculated The number of the subjects was 19 all of them medical students

Results

The results of the investigation are presented in a table and a scatter diagram

In the diagram each ring gives the value of tg 2 γ and mean value of K for one of the subjects The two fine lines on the diagram are the lines of regression calculated

The product moment correlation coefficient was calculated from the data It was found r = 0 66 This value is significant at the $P < 0\,01$ level

It seems established that there is a co variation between γ and K

The angle γ cannot by itself be the cause of the asymmetry of the horizontal subjective metric The two possible explanations of the asymmetry of the horizontal subjective metric are

1 An asymmetry of the distribution of the spatial values of retinal points
2 An asymmetry of the optical system of the eye such as angle δ or angle ε

Of those possibilities the second one agrees best with the present results A co variation between the angle γ and such optical asymmetries as the angles δ and ε is to be expected but there seems to be no reason to believe that the hypothetical asymmetry of the spatial values of retinal points should co variate with the angle γ

Summary

The asymmetry of the horizontal subjective metric measured by the bisectioning experiment of Kundt was correlated with the angle γ which gives an expres sion of the asymmetry of the optical system of the eye A statistically significant correlation was found

It was concluded that the asymmetry is caused not by an asymmetrical dis tribution of the spatial values of retinal points but by asymmetries of the optical system of the eye

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From The Department of Ophthalmology
Kommunehospitalet Copenhagen
(Heads P Brændstrup M D and M S Norn M D)
and The Laboratory of Clinical Immunology
Rigshospitalet Copenhagen (Head G Bendixen M D)

DELAYED HYPERSENSITIVITY IN HUMAN UVEITIS INVESTIGATED WITH THE LEUCOCYTE MIGRATION METHOD

BY

SVEND STRANDGAARD AND OTTO BRÆNDSTRUP

Abstract

Patients with endogenous uveitis were investigated for cellular hypersensitivity to antigenic components of bovine uveal retinal and kidney extracts by means of the leucocyte migration technique In most patients no antigen induced inhibition of *in vitro* migration of blood leucocytes could be demonstrated A few uveitis patients however showed a positive reaction with retinal antigen The possible significance of these results is discussed

Key words uveitis – delayed hypersensitivity – leucocyte migration test

Introduction

In human endogenous uveitis the importance of immune phenomena is frequently discussed and investigated Most studies have dealt with circulating antibodies in uveitis patients or experimental animals Thus precipitating anti

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bodies to human uveal antigen (Aronson et al 1966) and complement fixing and other antibodies to bovine uveal antigen (Hallet et al 1962 Luntz 1968) have been found in a high percentage of patients with endogenous uveitis Similar antibodies can be found in other eye diseases possibly secondary to inflammatory uveal involvement (Aronson et al 1966) and their importance in the development of human endogenous uveitis is open to question Besides uveal antibodies complement fixing antibodies to human liver and kidney antigen can be demonstrated in the blood of uveitis patients (Hallet et al 1962) Precipitating antibodies of this specificity do not seem to occur (Aronson et al 1966)

Experimental uveitis can be produced in various animal species by immunization with homologous uveal or retinal antigen (Aronson 1968 Wacker & Lipton 1968 a) less effectively with heterologous antigen (Aronson 1968 Wacker & Lipton 1968 a Luntz 1968) Many animals develop circulating antibodies together with the eye disease (Aronson 1968 Luntz 1968) In guinea pigs a delayed type skin reactivity has been shown to accompany experimental uveitis after immunization with homologous or heterologous retinal antigen (Wacker & Lipton 1968 b) Homologous and heterologous antigens did not cross react in the skin reaction contrary to what was found with circulating antibodies

The occurrence and significance of such delayed hypersensitivity reactions in human endogenous uveitis has not thus far been investigated In a survey Chandler (1969) suggests that cell mediated hypersensitivity might be of prime importance in the pathogenesis of that disease a hypothesis not yet supported by experiment

Antigen specific inhibition of the migration of immunocompetent cells is one of the newer in vitro mo[illegible] f delayed hypersensitivity It was applied as such a model by George & Vaughan (1962) based on the early observation of Rich & Lewis (1932) The migration technique has been modified by Bendixen & Soborg (1969) for use with human blood leucocytes and has made it possible to demonstrate organ specific inhibition of the in vitro migration of these cells in various diseases of a suspected autoimmune pathogenesis e g ulcerative colitis glomerulonephritis and idiopathic Addison s disease (Bendixen 1969 1968 Nerup et al 1969) In multiple sclerosis no such reactivity could be found with various central nervous system antigens (Strandgaard 1970 1971)

The aim of the present study was to investigate by means of the leucocyte migration technique the presence of cellular hypersensitivity to eye antigen in uveitis patients

Material and Methods

A total of 22 patients with uveitis were investigated 10 males and 12 females aged [illegible] 54 years (Table I) On usual clinical criteria 12 patients were classified

Table I
The uveitis patient material and the migration indices obtained with uvea retina and kidney antigen extract

Patient no	Sex	Age	Type of uveitis	Glucocort (S = systemic L = local)	Migration index antigen		
					Uvea 200 μg/ml	Retina 100 μg/ml	Kidney 100 μg/ml
1	M	37	recurrent active	O	0 89	1 08	
2	F	79	recurrent active	O	0 98	0 93	
3	F	60	recurrent active	O	0 98	0 79	0 95
4	M	49	recurrent active	L	0 99	1 02	0 99
5	F	26	recurrent active	L	1 05	0 99	
6	F	63	recurrent active	L + S	0 99	1 04	0 99
7	M	66	recurrent inactive	O	1 01	1 07	1 20
8	M	70	recurrent inactive	O	0 87	0 71	0 76
9	M	62	recurrent inactive	O	1 08	1 05	0 98
10	M	46	recurrent inactive	O	1 01	1 19	1 06
11	F	67	recurrent inactive	O	0 97	1 15	1 04
12	M	68	recurrent inactive	O	0 93	1 07	0 98
13	F	22	chronic	L	0 98	1 19	
14	F	50	chronic	L	1 24	1 26	1 29
15	F	53	chronic	L	0 95	1 01	1 02
16	F	61	chronic	L + S	0 92	1 06	0 88
17	F	56	chronic	L + S	1 04	0 89	1 01
18	F	71	chronic	S	1 20	0 81	0 87
19	M	63	chronic	O	1 07	1 16	1 17
20	M	84	chronic	O	0 95	1 04	1 01
21	F	41	chronic	O	0 9[illegible]	0 94	
22	M	66	chronic	O	1 08	0 94	1 0[illegible]
				Mean	1 0[illegible]	1 02	1 02

as having uveitis of the acutely recurrent type 6 of these were tested during an acute attack 3 within the first 24 hours before glucocorticoid had been given and 3 during systemic and/or local glucocorticoid treatment 6 patients were tested between attacks when no sign of clinical disease was present 10 patients were classified as having chronic uveitis 6 of these were under systemic and/or local glucocorticoid treatment at the time of blood sampling because of clinically active disease Blood samples for control experimentes were obtained from 20 persons without eye disease compatible to the uveitis patients in age and sex distribution

Bovine eyes and kidneys were obtained from freshly sacrificed animals Uvea and retina were isolated from the eyes by sterile dissection The tissues were chipped homogenized and eluted with Hanks balanced salt solution After centrifugation the supernatant was lyophilized and stored in closed ampoules at room temperature Before use the preparations were redissolved in distilled water and standardized through protein determination by means of a modified biuret reaction.

The leucocyte migration experiments were performed as described by Bendixen & Soborg (1969) Heparinized blood from a cubital vein was allowed to sediment for one hour at 37° C The plasma was withdrawn and the white cells were washed three times in Hanks balanced salt solution The cells (approximately 50 per cent granulocytes and 50 per cent lymphocytes) were transferred to capillary tubes and were allowed to migrate from the tube openings on the bottom of 1 ml tissue culture chambers The chambers contained TC 199 with 10 per cent horse serum and the migration experiments were performed at 37 C After 24 hours the circular migration areas were measured by paper planimetry The migration index (MI) was calculated in the following way

$$MI = \frac{\text{migration area of antigen containing culture}}{\text{migration area of antigen free culture}}$$

Thus values of MI less than 1 0 would indicate inhibition and more than 1 0 stimulation of migration

In the present study 100 or 200 micrograms (measured as protein) of uveal retinal and kidney preparations were added to the migration cultures of patients and controls

Results

Controls With uveal extract the normal range (mean ±2 SD) of MI was calculated on the basis of 71 examinations of 1 control persons without eye disease and was found to be 0 82 1 18 With retinal extract a normal range was calcu

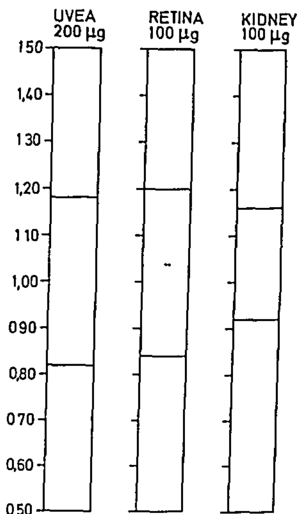


Fig 1

Migration index (MI) of blood leucocytes of uveitis patients when exposed to extracts of uvea, retina and kidney in the amounts of 200 100 and 100 micrograms protein per ml respectively Normal limits calculated from mean ± 2 SD of control persons

lated in a similar way as 0 84-1 20 based on 17 controls and with kidney extract 0 92 1 16 based on 7 controls

Uveitis patients The results are presented in Table I and Fig 1 A few uveitis patients had a slight inhibition of leucocyte migration with retinal and kidney extracts but none of the patients showed inhibition with uveal extract Of the three patients whose leucocyte migration was inhibited by retinal extract one had an acute attack of uveitis and did not receive glucocorticoid treatment at the time of examination Another suffered from recurrent attacks of uveitis but had no active disease at the time of study and the third patient received long term glucocorticoid treatment because of chronic uveitis

Discussion

From the results it is seen that only a few uveitis patients showed inhibition of *in vitro* leucocyte migration with retinal extract and that none did so with uveal extract There are some possible explanations of this mostly negative result of the study

It may indicate that no state of organ specific delayed hypersensitivity was present in the uveitis patients at the time of blood sampling Unfortunately we did not have opportunity to make serial investigations in the individual patients and we therefore do not know whether a positive migration test may occur as a transitory phenomenon only In some patients the immunological reactivity may have been suppressed by glucocorticoid therapy although a slightly positive test is noted in one patient in whom such therapy was given.

It may be that the species specific human eye antigens are needed to obtain a more consistent inhibition of leucocyte migration in uveitis patients As mentioned in the introduction homologous antigen is more effective than is heterologous antigen in producing uveitis in the experimental animal (Aronson 1968 Wacker & Lipton 1968 a Luntz 1968) On the other hand circulating antibodies to bovine eye antigen have been demonstrated in ome uveitis patients (Hallet et al 1962 Luntz 1968) indicating that cross reacting organ specific antigens actually occur

Another possible explanation of the mostly negative result of our study is that delayed immune processes in uveitis may be more or less confined to the eye The size of the reacting uvea may be too small for the detection of sensitized immunocompetent cells in the blood The finding of circulating antibodies to eye antigens in the blood of uveitis patients speaks against this possibility

Finally it may simply be that organ specific antigen has not been applied in available form in the test system However the method of preparation de cribed has yielded antigen containing extracts from a number of other organs in this laboratory e g kidney intestinal mucosa and adrenal cortex

It it interesting that all the cases who showed inhibition of leucocyte migration reacted to retinal extract and that no reaction to uveal extract was observed It is known that immunization with retinal antigen may produce uveitis in the experimental animal (Wacker & Lipton 1968 a) With kidney antigen some patients had inhibition of leucocyte migration No conclusion can be drawn fr m this fact since the control material is too small

Further studies in endogenous uveitis with the leucocyte migration test should be done with homologous as well as heterologous antigen and the patients should be followed over longer periods with repeated examinations

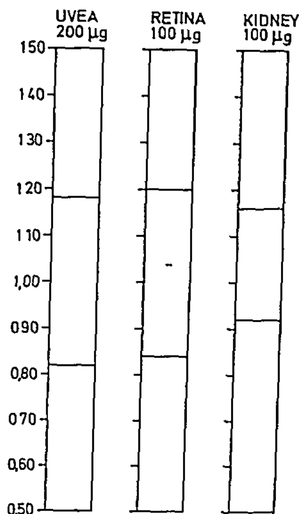


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The Department of Ophthalmology
(Head Prof Viggo A Jensen)
Kommunehospitalet University of Aarhus 8000 Aarhus C Denmark

ELEVATED TONOMETER READINGS CAUSED BY A THICK CORNEA

BY

F KRUSE HANSEN & N EHLERS

Borderline glaucomas represent a well known and difficult problem Has this patient glaucoma or is the elevated ocular tension an illustration of statistical variation?

During clinical studies of the central corneal thickness (Kruse Hansen 1971 Kruse Hansen et al 1971) a variation from 0 4 to 0 6 mm was found in different persons In the calibration of the applanation tonometer a corneal thickness of 0 5 mm is established With a normal variation about ± 20 per cent it was tempting to study the influence of variation in central corneal thickness upon the measured value of the intraocular pressure

Material and Methods

Eight patients suspected to have open angle glaucoma were studied Ophthalmological examination was made *including slit lamp examination gonioscopy ophthalmoscopy* and visual field *examination Central corneal thickness* was measured with the Haag Streit pachometer as previously reported (Ehlers & Kruse Hansen 1971) Intraocular tension was measured with the Goldmann applanation tonometer and the Schiotz indentation tonometer Further water drinking test was done

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The Department of Ophthalmology
(Head Prof Viggo A Jensen)
Kommunehospitalet University of Aarhus 8000 Aarhus C Denmark

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tension has responded but little upon the given antiglaucomatous treatment. These patients probably do not have glaucoma the elevated tonometer readings being accounted for by the thick cornea

Corneal thickness in verified cases of open angle glaucoma is not generally higher than normal (Ehlers 1970)

The present paper is a preliminary communication pointing out a new aspect of measuring ocular tension This may be of particular value in management of suspected glaucoma cases found by routine examination or in glaucoma screening

Summary

Eight patients suspected and treated for open angle glaucoma with slightly increased tonometer readings as the only objective finding were examined Central corneal thickness was significantly higher than normal This may be a possible explanation of a measured value of intraocular tension above normal in spite of a normal intraocular hydrostatic pressure

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ZUR KENNTNIS DER KERATOCONJUNCTIVITIS SICCA VIII

Uebersicht – Ätiologie

VON

HENRIK SJÖGREN

Die Hauptsymptome des Sicca Syndroms (Sjogrens Krankheit) sind Keratoconjunctivitis sicca – Xerostomie – chronische Polyarthritis Ausser den genannten Symptomen kommt weiter eine Reihe anderer mehr oder weniger haufiger Symptome vor

Betreffs dieser Symptome mochte ich auf meine vorige in dieser Zeitschrift veroffentlichte Arbeit hinweisen (Vol 46 1969 S 201)

Die Histologie der Tranen und Speicheldrusen habe ich in meiner Inaugural dissertation in Acta Ophthalm Suppl II 1933 ausfuhrlich beschrieben Es wird deshalb nicht notwendig sein darauf einzugehen bloss mochte ich den dabei typischen kraftigen Parenchymzerfall in Verbindung mit einer reichlichen Einwanderung von Lymphozyten teils auch von *Plasmazellen* hervorheben. *Um* die ursprungliche Entstehung dieser Veranderungen studieren zu konnen, wurden in ein paar Faller von ausgesprochener Keratoconj sicca doch ganz ohne Spur von xerostomie *probeexzidierte Stuckchen von der Parotis untersucht.* Die Ergebnisse sind in Acta Ophthalm 16 40 1938 veroffentlicht worden Im mikroskopischen Bild sieht man hier wie ein Teil der Drusenzellen ihre Grenzen verloren haben und wie sie als eine Protoplasmamasse mit unregelmassig verstreuten Kernen zusammenliegen Olhagen (1954) hat gezeigt dass die Ba

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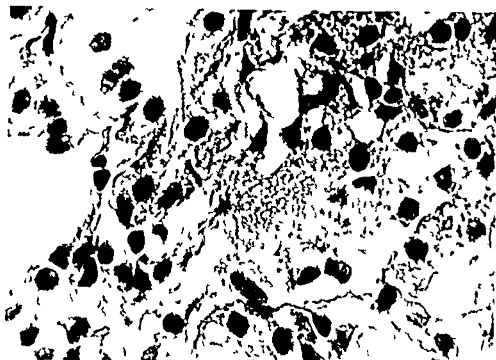


Fig 1
Beginnungsstadium der Drusenkrankheit
Parotis Unregelmassige Protoplasmamasse mit verstrauten Kernen

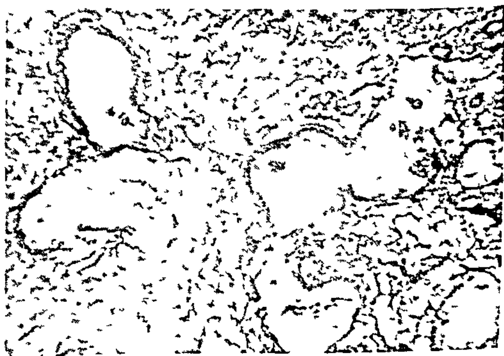


Fig 2
Nach Olhagen Proceed of the IV European Rheumat Congres Istanboul (1954)
Parotis Fragmentation und *Duplikation der Basalmembranen*

salmenbranen in der Parotis in *solchen Gegieten Fragmentation und Duplika* tion aufweisen.

Identische Bilder sind von Stuart und *Allen* (1958) in der Schilddruse bei Hashimotos thydeoiditis die auch beim Sicca Syndrom erscheinen kann nach gewiesen worden

Ernst Haas (1951) hat einen *Fall* von Sjogrens Syndrom obduziert wo der Patient in Urämie gestorben war Er fand dabei in der Parotis schwerste *Arteriosclerose* mit volliger *Zerstorung der Intima und der elastischen* Fasern In der Adventitia ein lockeres Granulationsgewebe an das sich ein stark rund zellig infiltrierter Bezirk anschliesst. *Submandibularis Sublingualis* und die Tranendrusen zeigten die gleichen Veranderungen des Drusenparenchyms In den Gefassen gab es eine *hochgradige Endarteritis produktiva* Die kleinen Speichelschleimdrusen der Zunge der Wangenschleimhaut Tonsillargegend und der Epiglottis liessen *mittelgradige* Entparenchymisierung *der Drusen* ausfuhrungsgange ohne Drusenacini und mit Endarteritis produktiva erkennen An der Nase und den Nasennebenhohlen bestand eine ausgesprochene *Dru senarmut und Fibrose* der Schleimhaut. Die epiglottis zeigte die gleichen Ver anderungen Im Uterus wurde atrophische Schleimhaut mit faserigem Stroma mit *verbreiteten Blutungen nachgewiesen* An den tiefer gelegenen *Arterien* astchen eine frische Endarteritis In den Nieren zeigten sich Gefasswand schaden erkennbar durch *Arteriosclerose* Am Pankreas frische *degenerative* Vorgange.

Seiner Schlussfolgerung nach haben alle *diese krankhafte Prozesse* klar rheu matische Ursachen Er betont auch die Vorteile einer Obduktion da dadurch ganze Organe untersucht werden konnen indem Sjogren nur Probeexzisionen zur *Verfugung standen.*

Beigelboch und Hoff (1952) hatten bei einer Gelegenheit die Moglichkeit, eine Obduktion *auszufuhren und fanden dabei* Atrophie in den Speichel und *Tranendrusen.* Sie verweisen weiter auf einen Fall der neulich von Bohm (1950) beschrieben wurde und der folgendes *zeigte* Schwere akute teils necrotisierende und *proliferierende* Endartheritis der kleinen bis mittelgrossen Arterien mit zahlreichen Granulomen Gefassverschlussen und *perivaskularen* Blutungen, sowie *punktformigen Blutungen* insbesondere in den beiden Nieren (maligne Nephrosclerose) sowie in der Haut, im Bauchfell in den Lymphkno ten den Speichel Schleim und Tranendrusen *und in der Uterusschleimhaut.* Hochgradige Coronarsclerose mit zahlreichen Herzmuskelschwielen und ge ringer *konzentrischer* Herzhypertrophie Mittelgradige *Sclerose der Aorta*

Der andere von Beigelboch und Hoff zitierte Fall hatte eine vollstandige Schwiele *Im Liquor* wurde Landy pos erkannt Die linke art. carotis *war vollig verstopft* durch einen alten organisierten *Thrombus* In der Wade wurden auch perivaskulare Infiltrate *entdeckt* bestehend aus Lymphozyten und Plasma zellen *und Fibroblasten,* ganz den Aschoff Knotchen *entsprechend* Die Haut

war etwas atrophisch mit sparlichen zersplitterten, elastischen Fasern Die Schweissdrusen waren sehr sparlich vorhanden An mehreren Stellen gab es Gefässveranderungen in der Form von kleinen Infiltraten rings um Arteriolen und Venolen aus Rundzellen und Fibroblasten bestehend Uebrige Gefasse zeigten Verdickung der Gefasswande Im Ganzen ein Bild in Uebereinstimmung mit rheumatischen oder allergischen Gefassveränedrungen Weiter waren sowohl Schweiss- als auch Talgdrusen angegriffen

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Jebovy Hradsky und Herout undersuchten die Magenschleimhaut und machten gastrobioptische Untersuchungen mit einer Saugbiopsiesonde wobei mikroskopisch eine chronische atrophische Gastritis in 59 % von 17 Fallen (1961) von Sicca Syndrom gefunden wurde Pittman und Holub (1965) machten Biopsien der *Schleimhaut* im Jejunum und fanden dabei eine *totale Atrophie* der Villi mit Abflachung der Epithelzellen Infiltration des Epithels und Lamina propria mit Rundzellen und Plasmazellen

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Heilesen (1962) fand in einem Fall die Rindenschicht der *Nieren* recht schmal, doch mit normalen Glomeruli. An zahlreichen Stellen gab es auch *fokale Lymphozyteninfiltrate in dem Rindengewebe*, besonders *subkapsular* und perivaskular, was als *pathologisch bezeichnet werden muss*. Er fand auch eine leichte Atrophie der *Nebenniere* in der *Rindenschicht* mit leichten Degenerationen der Rindenzellen und stellenweise dichte fokale Lymphozyteninfiltration, einzelne Plasmazellen aber keine Keimzentren oder Granulozyten. Aus Heilesens Werk ist weiter hervorzuheben, dass er die *Hypophyse* von einer beträchtlichen Lymphozyten- und Plasmazellinfiltration umgeben fand und dass er im *Knochenmark* eine Anhäufung von Lymphozyten und vielen Plasmazellen, besonders in Beziehung zu den Kapillaren, nachgewiesen hat.

Das Gleiche ist auch von Kaltreider und Talal (1969) nachgewiesen worden.

Block und Bunim (1963) wiesen in 4 Fällen vom Sicca Syndrom Hyposthenurie nach. Diese hatte ihren Grund in mangelhafter Wasserpermeabilität und wurde durch Infiltration von Lymphozyten und Plasmazellen in der Nierenmedulla erklärt. Solche Infiltrationen sind auch von Bucher und Reid (1959) rapportiert worden.

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Klinische Symptome bei chronischer interstitieller Nephritis sind, wie es sich herausgestellt hat, beim Sicca Syndrom recht reichlich vorkommend und man hat sie in diesen Fällen mit einer verschlechterten Konzentration des Urins in Verbindung gesetzt. Keine aktive Pyelonephritis liess *sich aber nachweisen*.

Tu Shearn et al. studierten die interstitielle Nephritis bei Sjögrens Syndrom (1968) mittel Biopsie in 8 Fällen und durch Obduktion in einem Fall. Samtliche hatten Proteinurie. Nach histologischer Untersuchung haben sie festgestellt, dass interstitielle Nephritis die hauptsächliche renale Läsion bei Sjögrens Krankheit ist.

Hradsky et al. fanden nekrotische Arteriitis in der Leber und der Schilddrüse and Bunim (1961) fand Splenomegalie in 10 Fällen und Hepatomegalie

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in 8 Fallen Rayneauds Krankheit war in 7 Fallen vorhanden und in 7 Fallen konnten mit Rtg pleurale Verdickungen nachgewiesen werden

Eine sehr gute und vollständige Zusammenstellung der Symptomatologie findet sich in einer Arbeit von Block Buchanan Wohl und Bunim in Medicine 44 187, 1965

Neuropathie ist fruhed von Attwood und Poser (1961) erwahnt worden. Kaltreider und Talal haben unter ihren 109 Fallen die uber 10 Jahre gesammelt sind 9 gefunden mit dokumentierter periferer Neuropathie

Im Ganzen sind demnach drei Falle von akuter oder chronischer *Vasculitis* nachgewiesen worden Bei der postmortem Untersuchung des sensorischen Trigeminuskernes in einem Fall gelang es nicht Inflammation nachzuweisen trotz der verbreiteten Vasculitis in anderen Teilen des Gehirns Was die Muskeln betrifft zeigte sich bei 9 Fallen von 10 Muskelbiopsien aktive Vasculitis An einem Patient bei dem Vasculitis fehlte entdeckte man statt dessen Vasculitiden in der Haut

Kaltreiter und Talal (1959) "The presence of neuropathy correlated strongly with vasculitis in the nerves and muscles *The vascular inflammation was felt to be causally related to the pathogenesis of the neuropathy* "

Good und Mitarbeiter (1965) haben neulich eine diffuse subklinische periphere Neuropathie bei rheumatischer Arthritis als gewohnlich festgestellt Das patologische Bild zeigt akute und chronische Vasculitis in und ringsum den Nerven mit fleckigen Stätten von Myelindegeneration

Das Bild der periferen Neuropathie bei Sjogrens Syndrom ist nach meiner Meinung identisch mit dem der rheumatoiden Arthritis

In einem Fall von Sicca Syndrom das zum Tode gefuhrt hat haben Cardell und Gurling Autopsie gemacht und dabei „vasculare Lasionen typisch fur Polyarteriitis nodosa in beiden Nieren beiden Nebennieren und in der Leber der Milz dem Pankreas Dunndarm und Dickdarm und dem Myokard nachgewiesen In einem anderen Fall zeigte eine histologische Untersuchung wohl entwickelten obliterative Endarteriitiden

Ramage und Kinnear (1954) rapportierten uber einen Fall von Sicca Syndrom assoziiert *mit Polyarteriitis nodosa disseminiertem Lupus erythematodes* und Sclerodermie Sokoloff und Bunim haben einen Fall von Sicca Syndrom veroffentlicht wo man bei Biopsie des Sartoriusmuskels Veranderungen der Arterien fand die typisch sind fur Polyarteriitis nodosa

Szanko Farkas und Gyulai (1952) notierten beim Obduzieren eines Falles perineurale und intraneurale Rundzelleninfiltration ahnlich der im Gefassystem vorkommenden doch ohne klinische Zeichen neurogener Veranderungen

Cruickshank (1954) fand bei Obduktion von 72 Fallen rheumatischer Arthritis Arteriitissymptome in 18 Fallen Die Symptome kamen im Uebrigen vom Herz und den periferen Nerven und Muskeln Kemper Baggenstoss und Slo

cumb wiesen bei Obduktion von 52 Fallen rheumatoider Arthritis Arteriitis in 12 Fallen nach Ball (1954) hat 4 Patienten mit typischer rheumatoider Arthritis bei denen Autopsie Polyarteriitis nodosa in den *meisten Viscera* zeigte beschrieben In gleicher Weise wie *vasculare Lasionen als Komplikationen der rheumatischen Arthritis gefunden* worden sind sind auch Rapporte uber *perifere* Neuropathien bei dieser Krankheit eingenkommen Irgy Adams und Toone (1958) haben 6 Falle von rheumatoider Arthritis beschrieben mit periferer Neuritis in den unteren Extremitaten in samtlichen Fallen in den oberen Extremitaten in 3 Fallen Hart, Golding und Mackenzie (1957) fanden in einem Fall ausgesprochene Neuropathien und glaub en die *Arteriitis sei die Ursache der Arthritis* Kemper fand in 4 Fallen klinische Zeichen periferer Neuropathie wobei sich bei der Autopsie Angitis ringsum den periferen Nerven herausstellte

Aus diesem folgt dass die Neuropathien gleich wie die Vasculitiden als Komplikationen einer rheumatischen Arthritis bezeichnet werden mussen Das Antreffen polyarteriitischer Lasionen bei rheumatischer Arthritis die craniale und perifere Neuropathien zur Folge haben ist wohldokumentiert Diese Tatsache ist von grossem Interesse hinsichtlich des Falles von Attwood und Poser bei dem multiple craniale Nervenparalysen nebst periferen Neuropathien observiert wurden Dass der Patient dazu noch die typischen Sicca Symptome aufgewiesen hat scheint ein Beweis dafur zu sein dass *eine starke Verbindung zwischen den beiden Krankheiten rheumatischer Arthritis und dem Sicca Syndrom existiert* In Anbetracht der atiologischen Bedeutung der Veranderungen in den kleinen und mittelgrossen Blutgefassen fur die Entstehung der Drusenkrankheit drangt sich die Frage hervor ob ahnliche Gefassveranderungen etwa die gleiche Bedeutung fur das Entstehen der Arthritiden haben Bunim et al (1964) haben aber gezeigt dass diese Symptome Vasculitis mit Neuropathie und Myopathie ohne klinische Zeichen der Arthritis vorkommen konnen

Es ist in mehreren Fallen angegeben worden dass man bei Patienten mit dem Sicca Syndrom auch Raynaud s Krankheit und Sclerodermie gefunden hat Mikroskopisch sieht man bei Sclerodermie Lymphozyten und Plasmazellen ringsum den Gefassen Die Gefasswande sind sehr verdickt zuletzt werden die kleinen Gefasse durch obliteration vollig zugeschlossen und die Haut wird atrophisch Raynaud s Krankheit pflegt wie pekannt in Sclerodermie zu ubergehen

Klinisch besteht die Krankheit – sowohl das Sicca Syndrom als auch die chronische Arthritis – in einer langen Reihe von Gefassveranderungen mit davon bedingten Rundzelleninfiltrationen und Zerfall der angegriffenen Drusen Diese scheinbar primare Gefassschadigung liegt offenbar wenigstens im Anfang in den kleineren periferen Verzweigungen Dies lasst sich u a daraus schliessen dass der Angriff auf die Drusen mit nur einem Drusenlobus an

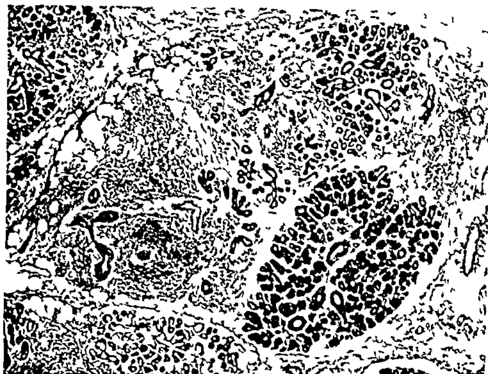


Fig 3
Nach Block Buchanan Wohl und J Bunim Medicine (1965) 44 187
Ein Lobus ganz gesund wahrend die anderen mehr oder weniger angegriffen sind

fangt wahrend dessen die anderen anfangs gesund bleiben Wenn dann ein anderer Lobus angegriffen wird erkrankt in der Regel nicht der ganze Lobus sondern erst nur die zentrale Partie Dies kann man an der nebenstehenden Figur 3 sehen wo ein Lubus ganz gesund ist wahrend die anderen mehr oder weniger angegriffen sind Ich habe selbst einen identischen Fall Dass der Lobus nicht auf ein Mal im ganzen erkrankt ist von vielen Autoren hervorgehoben worden

Ein anderer Umstand auf den ich hier hinweisen mochte ist der das der rheumatische Faktor von den autoimmunen Reaktionen bei Sicca Patienten wesentlich starker hervortritt wenn die Anthritis nicht vorhanden ist dass er aber wesentlich schwacher wird wenn die Arthritis sich ankundigt

Da haben wir nun in den kleinen und eventuell in den mittelgrossen Gefassverzweigungen den vielleicht gemeinsamen Grund sowohl des Sicca Syndroms als der chronischen rheumatoiden Arthritis Das beinahe ausschliessliche Vorkommen der Sicca Krankheit bei Frauen zeigt hier dass ein endokriner Faktor eine wesentliche Rolle spielt

Zusammenfassung

Die Erfahrungen aus den letzten Jahren zusammen mit Untersuchungen aus fruheren Jahren haben gezeigt dass in den kranken Drusen die kleinen Blutgefasse d h. Arteriole Venolen und Kapillaren mit Verdickung und fibrinoser Degeneration der Wande und schliesslicher Thrombosierung erkrankt sind

Alle diese Veränderungen sind auch in Fallen von chronischer Polyarthritis nachzuweisen Man hat hier auch Neuritis erkannt wo der angegriffene Nerv von Rundzellen umgeben ist gleich wie in Fallen des Sicca Syndroms sogar ohne Zeichen gleichzeitiger Arthritis Man hat weiter oft Vasculitis und Rundzelleninfiltration rund um die kleinen Gefässen beobachtet Ja man hat solche Statte auch in den Muskeln wie in den meisten inneren Organen angetroffen.

Hierdurch erhalt die Verbindung zwischen dem Sicca Syndrom und der chronischen Polyarthritis eine Erklarung

In meiner fruheren Arbeit habe ich das Sicca Syndrom als einen Ausdruck fur allgemeine Adenopathie auf autoimmuner Basis beschrieben Dass die Veranderungen im Anfang der Drusenkrankheit einen autoimmunen Prozess als Folge haben konnen durfte offenbar sein

Seit langem hat man im Blut LB Zellen nachweisen konnen und seit ein paar Jahren sprechen deutsche Forscher von Sjogren Zellen d h falsche LB Zellen die im Blut beim Sicca Syndrom auftreten (Baumer 1963 Urbaszek et al 1970)

Wir haben also gefunden

Falle von chronischer rheumatischer Arthritis weisen oft Arteriolitis Venolitis und Kapillaritis an verschiedenen Stellen und in verschiedenen Organen auf

Falle von Sicca Syndrom leiden oft auch an Arthritis und haben dann auch die gleichen Veranderungen in den kleinen Gefassen

Falle von Sicca Syndrom kommen nicht selten ohne irgendwelche Zeichen der Arthritis vor Auch in solchen Fallen sind aber die gleichen Gefass veranderungen vorhanden

Die gleichen Gefassveranderungen treten also bei beiden Krankheiten auf und konnen da sogar fruher erscheinen als Veranderungen in Drusen oder Gelenken

Infolge dessen betrachte ich die Ätiologie des Sicca Syndroms als eine Kreislaufstorung in Verbindung mit autoimmunen Prozessen in den verschiedenen Drusen

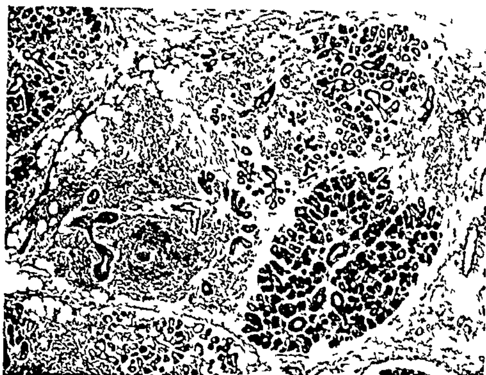


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on a dish that was kept on ice in a thermos flask for up to 2 hours The various parts of the eyes were then dissected under as sterile conditions as possible and all tissues were kept frozen at –26° C for up to 3 weeks before extraction

Extraction procedures Proteins were extracted from bovine corneal epithelium by ultracentrifugation as described previously (Berger 1969) The lens proteins were extracted after removal of the lens capsule Extraction of proteins from the cortical layer was then performed by ultracentrifugation by filling up the perspex tube (Berger 19/0) with 80 μl distilled water and 200 mg of lens protein (wet weight) placed over the water layer After ultracentrifugation a water clear solution with a protein concentration of about /0 mg/ml was obtained The yield of proteins by this procedure was similar to that obtained by extraction following homogenization (Berger 1969)

Extracts from other tissues were obtained by homogenization as described previously (Berger 1969) The extracts were cleared by ultracentrifugation at °0 000 r p m for 30 minutes and an estimate of the protein concentration was obtained by the Folin test (Lowry et al 19ɔ1) the standard curve was constructed using a solution of proteins from bovine corneal epithelium where the nitrogen content was determined by the micro Kjeldal technique assuming the protein concentration to be 6 25 times the nitrogen value The following extracts were used the protein concentration is indicated in parentheses lens (/0 mg/ml) iris (13 mg/ml) choroid (19 mg/ml) vitreous (no water added) (18 mg/ml) retina (10 mg/ml) brain (10 mg/ml) skin (10 mg/ml) thyroid (100 mg/ml) adrenal gland (24 mg/ml) cardiac muscle (1ɔ mg/ml) skeletal muscle (24 mg/ml) lung (34 mg/ml) jejunum and ileum (21 mg/ml) liver (100 mg/ml) kidney (4° mg/ml) and testis (12 mg/ml)

Antisera To characterize the electrophoretically heterogeneous antigen (antigen 9) of bovine corneal epithelium (Berger 1971) a particularly potent antiserum was used this antiserum was prepared by immunization of a rabbit (R618) in the following way 2ɔ0 μl of bovine corneal epithelial extract of protein concentration 60 mg/ml prepared by ultracentrifugation (Berger 1969) was left for 3 hours at 37 C to aggregate spontaneously as described earlier (Berger 1971) The precipitate was collected by centrifugation and washed once in phosphate buffered saline before immunization It was dissolved in 1 ml of distilled water and mixed thoroughly with 1 ml complete Freund s adjuvant containing *Mycobacterium butyricum* (Difco Laboratories Detroit Mich cat No 0638–59) The injections were made at multiple intradermal sites as described previously (Berger 19/1) A booster dose was given 7 weeks later employing a similar dose of aggregated protein without the addition of adjuvant Ten days later the rabbit was bled for preparation of serum

In double diffusion tests in gel against an extract of bovine corneal epithelium

From Section of Immunology (Head Docent Morten Harboe M D)
Institute for Experimental Medical Research University of Oslo
Ulleval Hospital Oslo 1 Norway

DEMONSTRATION OF A TISSUE SPECIFIC ANTIGEN IN BOVINE CORNEAL EPITHELIUM BY IMMUNODIFFUSION

BY

BJORN BERGER

To study the relation between antigens of cornea and other tissues within the same species earlier investigators have used antisera prepared against crude extracts of cornea or corneal epithelium The antisera were used unabsorbed or absorbed with plasma in gel diffusion tests against extracts of other tissues and cross reacted with various other extracts Common antigens in cornea and other ocular and extra ocular tissues have thus been demonstrated whereas tissue specific antigens in corneal epithelium have not been described previously (cf Faure 1964 Witebsky 1965)

In a previous investigation (Berger 1971) antisera were prepared that reacted specifically with various protein fractions in extracts of bovine corneal epithelium In the present work such antisera were used in an attempt to demonstrate tissue specific antigens in bovine corneal epithelium It was found that a particular antigen termed antigen 9 characterized by electrophoretic heterogeneity and a great tendency to spontaneous precipitation from aqueous solutions was specific for bovine corneal epithelium

Material and Methods

Collection of samples The bovine organs were obtained 10–15 minutes after the death of the animals They were rinsed carefully in 0 9% NaCl and put

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other than corneal epithelium. The second precipitin band closer to the antibody well was rather diffuse Similar tests showed that this precipitin band was due to the reaction of antibodies with antigen 10 of bovine corneal epithelium (*main fraction*) The antiserum also contained weak precipitating antibodies against antigen 8 and antigen 13 that could be demonstrated by immunoelectrophoresis The precipitin lines due to these antibodies disappeared however within the heavy precipitate with antigen 10 in the double diffusion tests and thus did not interfere with the interpretation of the gel diffusion tests

The sensitivity of gel diffusion tests using this antiserum for demonstration of the electrophoretically heterogeneous antigen (antigen 9) was evaluated in the following way serial twofold dilutions of a fresh extract of bovine corneal epithelium of protein concentration 60 mg/ml were tested in double diffusion tests against antiserum R618 A definite precipitin line was obtained at all concentrations tested down to 1 9 mg/ml The next dilution of the extract, containing 0 95 mg protein per ml did not give a distinct precipitate but induced deviation of the immune precipitate of the neighbouring well Previous experiments indicated that antigen 9 constitutes approximately 20 per cent of the protein of fresh extracts of bovine corneal epithelium (Berger 1969) By using this antiserum in gel diffusion tests where the set up permits detection of deviation of the precipitin line the sensitivity of the test system is thus in the order of 0 2 mg/ml of antigen 9

The double diffusion tests in gel were made as previously described (Berger 1971) In tests for antigen 9 in other tissue extracts with antiserum R618 all tests were set up with an extract of bovine corneal epithelium in the neighbouring well so that tests were both for direct precipitation and for deviation of the precipitin line (cf Fig 2)

The antisera against antigens 8 10 and 13 were those previously described (Berger 1971)

Search for antigens in other tissue extracts Both direct precipitin tests and absorption experiments were made to demonstrate antigens 8 9 10 and 13 of bovine corneal epithelium in the other tissue extracts

Direct precipitin tests were made by double diffusion tests in agarose gel When antigen 9 was searched for each extract was tested in a system containing an extract of bovine corneal epithelium in the neighbouring well to permit analyses of deviation of the precipitin line For absorption of antisera 0 3 ml tissue extract was placed in a perspex tube described earlier (Berger 1970) The tissue extract was then lyophilized in the cold while in the perspex tube Subsequently 0 05 ml of antiserum was added the viscous mixture was stirred with a wooden spatula and carefully shaken for 30 minutes at 37° C It was then subjected to ultracentrifugation for 30 minutes at 4° C at 30 000 r p m in a

this antiserum produced two precipitin lines Fig 1 shows that the sharp precipitin line closest to the antigen well fused with a reaction of identity with the single precipitin line obtained using a specific antiserum against the electrophoretically heterogeneous antigen (antigen 9) placed in a neighbouring well This specific antiserum has previously been described in detail (Berger 1971) This precipitin line was very distinct with a characteristic position and the antiserum R618 was therefore used unabsorbed to obtain as potent a reagent as possible The specific anti 9 antiserum was used to define the corresponding precipitin line given by the potent serum R618 It was considered to be too weak to be used as a reagent to detect small amounts of antigen 9 in tissues

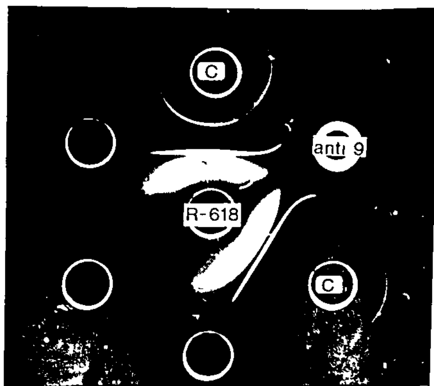
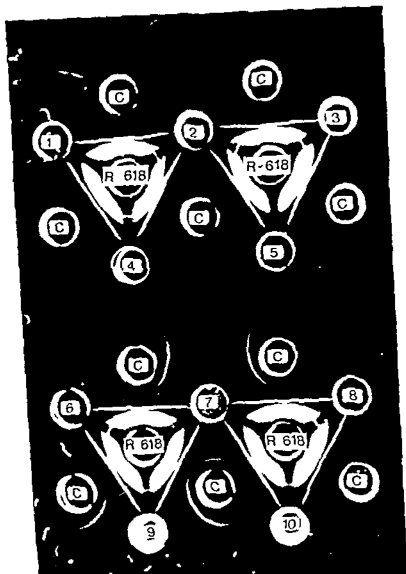


Figure 1

To identify the precipitin line due to reaction between antibody in serum R618 and antigen 9 of bovine corneal epithelium R618 Unabsorbed antiserum against antigen 9 of bovine corneal epithelium anti 9 Specific antiserum against antigen 9 C Fresh extract of bovine corneal epithelium protein concentration 60 mg ml The circular precipitin line is due to spontaneous precipitation of protein The diffuse precipitin line close to the central antibody well is due to the reaction between contaminating antibodies mainly anti 10 and the corresponding antigens



F gure ⁹

To show that anti 9 antibody in serum P618 gives a narrow sharp precipitin line with a fresh extr ct of b vine corneal epithelium but no precipitin line with 10 other tissue ext acts The extracts were 1 lens ⁹ choro d 3 kidney 4 iris 5 vitreous 6 skin 7 cardiac mu cle 8 adrenal gland 9 liver 10 thyro d. The precipitin line emerging from the cent al reg on of the thick precipitate in some instances is probably due to reaction with ant gen 13 present both in bovine corneal epithelium and the other extracts

Spinco model L50 ultracentrifuge equipped with a SW39 swinging bucket rotor After ultracentrifugation the supernatant was pipetted off and immediately used in gel diffusion experiments to test for remaining precipitating antibodies

Results

Fig 2 shows the results when 10 different tissue extracts were tested by double diffusion tests with antiserum R618 in comparison with a fresh extract of bovine corneal epithelium The thin immune precipitate closest to the antigen well containing the extract of corneal epithelium (c) is the immune precipitate due to antigen 9 the electrophoretically heterogeneous antigen It may be seen that this antigen was not found in the ten other tissue extracts illustrated in the figure These antigen wells were refilled twice the extracts did not precipitate with the anti 9 antibody nor was any deviation of the antigen 9 precipitin line observed Similar results were obtained with the other six tissue extracts tested

The antiserum gave a second big precipitin line with the bovine corneal extract and in some instances a faint precipitin band with the organ extracts The latter line did not show any immunological relationship to antigen 9

Extracts from lens liver cardiac and skeletal muscle were then tested by absorption of antiserum R618 None of them were able to remove the anti 9 antibodies from this antiserum Both the precipitin tests and the absorption experiments thus indicated that antigen 9 is specific for bovine corneal epithelium

An antiserum precipitating with antigen 8 of bovine corneal epithelium was tested with extracts of iris brain cardiac muscle skeletal muscle jejunum and ileum liver kidney adrenal glands and testis This antiserum gave a distinct precipitate with liver extract it precipitated weakly with kidney extract but not with the other extracts All anti 8 activity could be absorbed with the liver extract Thus this antigen is not tissue specific

An anti 10 antiserum was tested with the same extracts by double diffusion in gel It gave a faint precipitin line with the extracts from brain cardiac muscle jejunum and ileum and testis The antiserum was subsequently absorbed with the liver and lens proteins but the antibody activity remained Lack of precipitation thus corresponded to lack of absorbing capacity in these two extracts

Finally an antiserum reacting with antigen 13 of bovine corneal epithelium was tested with the same extracts It gave a strong precipitin line with all nine extracts and the anti 13 activity was removed by absorption with liver extract

tissue incorporated in complete Freund's adjuvant, and were absorbed with human serum and liver and kidney extracts. The tissue specific antigens were then defined on the basis of positive precipitin reactions between the absorbed antisera and extracts of prostatic tissue whereas the antisera did not precipitate with the materials used for absorption or with extracts of cardiac and pulmonary tissue. Negative reactions should always be evaluated considering the sensitivity of the methods used and the protein concentration of the tissue extracts. The protein concentration of such extracts differs considerably in the experiments reported earlier but has generally been in the order of 10–25 mg/ml (Aoki & Fujinami 1966, Aoki et al. 1969, Ablin et al. 1970).

In the present experiments the antiserum R618 – which precipitates with the electrophoretically heterogeneous antigen 9 of bovine corneal epithelium – was tested with extracts from 16 other tissues, five of these being from other ocular components and 11 from extra ocular tissues with protein concentrations varying from 10 to 100 mg/ml. The anti 9 reactions were consistently negative and additional experiments showed that the sensitivity for detection of antigen 9 in an extract was about 0.2 mg protein/ml. The absorption experiments were also negative and it was therefore concluded that antigen 9 of bovine corneal epithelium was tissue specific.

Most studies of tissue specific antigens have been made using double diffusion tests in gel and immunoelectrophoresis techniques that are semi quantitative and rather few considerations have been made concerning specific quantitation of various antigens in different organ extracts. Tissue specificity is said to be relative (Aoki et al. 1969) indicating that the term might also be applied for an antigen being present in high concentrations in one organ and in very low concentration in extracts from other organs. Fraction 10 (main fraction) constitutes about 30 per cent of the total protein in a fresh extract of bovine corneal epithelium (Berger 1969). A specific antiserum against antigen 10 of bovine corneal epithelium gave a faint precipitin line with extracts from brain, liver, testis and cardiac muscle which would indicate that the antigen is present in low concentration in these extracts.

Antisera against antigens 8 and 13 precipitated various other extracts, thus showing that these antigens are common to bovine corneal epithelium and other tissues.

Antigen 9 of bovine corneal epithelium has many distinctive features. It is electrophoretically heterogeneous, shows a marked tendency to spontaneous precipitation from aqueous solutions of high protein concentration and is a very potent hetero antigen (Berger 1969, 1971). A key question is whether this antigen also is a potent auto antigen. One would expect that tolerance to a

Discussion

To characterize the relationship between antigens of cornea and other organs previous authors have used antisera prepared against total extracts of cornea or corneal epithelium

Van Alphen & Robinette (1961) prepared antisera against total extracts of bovine corneal epithelium and tested their antisera against various extracts from bovine eyes and skin The antisera precipitated with extracts of corneal stroma and lens but not with extracts of lens capsule conjunctiva vitreous, retina, choroid or skin

Halbert & Ehrlich (1962) produced duck antisera against extracts of rabbit cornea and absorbed the antisera with rabbit serum prior to gel diffusion tests against serum and extracts of cornea heart liver brain and kidney Absorbed antiserum did not precipitate rabbit serum it gave 4 precipitin lines against cornea extract and precipitated kidney extract apparently with reactions of identity with 3 of these lines

Nelken & Nelken (1962) produced hen antisera against rabbit corneal homogenates and rabbit antisera against human corneal homogenates The antisera were absorbed with washed rabbit and human red cells respectively The authors claim to have demonstrated organ specific antigens in cornea through the use of tannic acid hemagglutination complement fixation and gel diffusion tests The data are difficult to interpret since the antisera were not systematically absorbed with serum and no illustrations appear in the published text

Perkins & Wood (1963) prepared rabbit antisera against a total extract of guinea pig cornea After absorption with normal guinea pig serum the antisera did not precipitate with serum but precipitated with extracts of cornea lens vitreous liver and kidney

Faure (1964) reviewed earlier reports and described his experiments with antisera against total extracts of cornea Some of the antisera have been absorbed insufficiently and most have been tested with a small number of extracts from other tissues Precipitin reactions have been observed between absorbed antisera that do not react with serum proteins and extracts of cornea and other ocular and some extra ocular tissues The experiments thus revealed antigens common to cornea and various other tissues but the data were insufficient to demonstrate tissue specific antigens in corneal epithelium

Criteria generally accepted as valid for demonstration of tissue specific antigens have not been established In a detailed study of tissue specific antigens of normal human prostatic tissue by Ablin et al (1970) the antisera were produced by immunizing rabbits with saline extracts of normal human prostatic

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tissue specific antigen of corneal epithelium might not be strong and that damage to the epithelium with liberation of such an antigen might result in autosensitization It is a fascinating hypothesis that immune reactions directed against such an antigen might induce tissue damage in the cornea and thus be of pathogenetic importance in chronic keratitis The pathogenesis of clinically important forms of chronic keratitis – like disciform keratitis following acute infections by *Herpes simplex* virus – is not yet understood (cf Laibson 1970)

Summary

To identify tissue specific antigens in bovine corneal epithelium antisera against the electrophoretically and antigenically distinct fractions 8 9 10 and 13 were tested in gel diffusion and absorption experiments with extracts of 5 other ocular and 11 extra ocular tissues

Antigen 9 of bovine corneal epithelium which is electrophoretically hetero geneous shows a marked tendency to spontaneous precipitation from aqueous solutions and is a potent hetero antigen could not be demonstrated in the 16 other tissues It is therefore concluded that this antigen is a tissue specific antigen of bovine corneal epithelium

Antigens 8 and 13 were demonstrated in several extra ocular tissues and are obviously not tissue specific The precipitin reactions between anti 10 and some extra ocular tissues were faint indicating that this antigen is present in very low concentration in these tissues

Note added in proof In addition to the extracts mentioned another extract was prepared by homogenization of corneal tissue which contained endothelium and stroma and from which the outer one third of the stroma and the epithelium had been removed The extract was tested at a concentration of 6 5 mg/ml against unabsorbed antiserum R 618 Antigen 9 could not be traced in this extract

Acknowledgement

The author is indebted to Docent Morten Harboe for valuable advice during the work

force causes the second *ascending portion of the record* The distance between the lowest point of the notch and baseline of the record has been correlated with intraocular pressure

Stepanik (19/0) by observation of ocular anterior segments through a trans parent chamber has found that the notch occurs when the *cornea is flattened to a diameter of about 5 mm We have reached a similar* conclusion by means of different experimental methods.

Material and Methods

The Mackay Marg tonometer mounted on a balance arm was described pre viously (Moses 1966) The mount and its chain device allowed us to vary the *total effective force on the tonometer in a uniform manner Enucleated human* eyes were cannulated through the sclera the needle entering the anterior cham ber between iris and lens and connected to a pressure transducer and constant pressure servoperfuser Three eyes were tested with similar results

The eye was perfused at an arbitrary pressure *(20 mm Hg)* while the tonom eter probe was slowly advanced *against the cornea* The *records* were of *fluid* withdrawn and of tonometer plunger displacement (Fig 1)

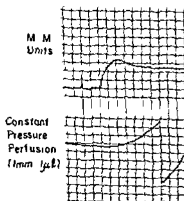


Fig 1
The tonometer probe was slowly advanced against the cornea of an eye maintained at 0 mm Hg by a servoperfuser Upper record Tonometer plunger displacement Lower rec rd Volume change Perfusion before tonometer application, downward slope at left Upward slope (interrupted by *automatic reposition*) withdrawal of fluid as tonom eter is advanced

From the Department of Ophthalmology
Washington University School of Medicine 660 South Euclid Avenue
Saint Louis Missouri 63110 U S A

THE MACKAY-MARG TONOMETER
A Note on Calibration Methods

BY

ROBERT A MOSES & WALTER J GRODZKI Jr

The Mackay Marg tonometer (Moses et al 1962) consists of a 1 5 mm diameter plunger mounted in the center of a flat footplate The tip of the plunger is nearly coplanar with the footplate projecting only a few microns beyond it The plunger is held in position by elastic elements made originally of silicone rubber but later of steel web springs Micromovements of the plunger relative to the footplate are electronically amplified and are recorded on a strip chart The tonometer is thus a force transducer

The typical recording obtained as the tonometer probe is advanced against the cornea consists of a rising line indicating increasing plunger displacement The ascent of the line is interrupted by a notch or brief recoil of the plunger followed by increasing rise so long as the probe is advanced toward the eye

Explanation of the record is that the advancing plunger at first supports intraocular pressure over the area of cornea flattened by the plunger plus the force required to bend the cornea As the probe is advanced and the flattened area enlarges the corneal bending force is transferred to the footplate At this point the plunger relieved of the bending force recoils slightly producing the dip or notch in the record Further advance of the probe increases intraocular pressure on the area of cornea supported by the plunger and this increasing

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FRIEDENWALD 1955 NOMOGRAM FOR SCHIOTZ TONOMETER

PRESSURE MILLIMETERS MERCURY

RIGIDITY COEFFICIENT

VOLUME OF INDENTATION CUBIC MILLIMETERS

Fig 3

Mackay Marg (M M) record (Fig 2) superimposed on ocular rigidity slope (F) This figure approximates closed manometer or clinical conditions Dip in tonometer record is found at a volume displacement of about 4 μl

independent of applanation area This diameter was found to be about 6 mm (Our earlier findings (Moses 1967) indicated an applanation diameter of 5 6 mm)

The second topic concerns the applanation diameter corresponding to the dip in the Mackay Marg record when the tonometer is used in its usual function in the clinical measurement of intraocular pressure In the present study we calculate that the dip is at applanation diameter of 5 mm in agreement with the findings of Stepanik (19 0) At the dip in the tonometer record we calculated that actual intraocular pressure is about 8 mm higher than steady state pressure. (The earlier study (Moses 1967) found the pressure 6 , mm above uninstrumented pressure by direct measurement.)

The main point to be drawn from these experiments is that the calibration of the Mackay Marg tonometer must be related to its use If the tonometer is to be

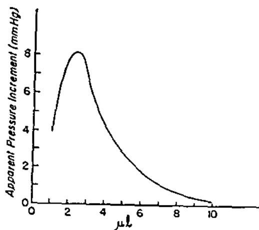


Fig 2
Height of tonometer record (in mm Hg) above final level as a function of volume displaced Derived from Fig 1

Results

The tonometer record (Fig 1) rose sharply to a peak above its final equilibrium level as the tonometer was forced against the eye The height of this peak above the final level plotted against displaced volume is shown in Fig 2 The record indicates that some component of corneal bending force acts against the tonometer plunger until more than 8 μl of displacement has occurred corresponding to an applanation diameter of about 6 mm in a cornea of average radius of curvature

Discussion

The results refer to interpretation of Mackay Marg tonometer indication under constant pressure conditions When the instrument is used to measure pressure in the living eye ocular pressure increases during tonometer application as the cornea is progressively distorted In this case tonometer scale reading (converted to mm Hg) is superimposed on the actual pressure increase of the eye This superimposition has has been plotted in Fig 3 for an eye of initial pressure 20 mm Hg and average ocular rigidity (0 0215) The trough or dip in the tonometer records is at 4 μl corresponding to an applanation diameter of 5 mm It is noted that the dip in the record occurs at this point even though some corneal bending force still is supported by the plunger

Two separate topics have been considered The first of these is the diameter of applanation required for corneal bending force on the plunger to become

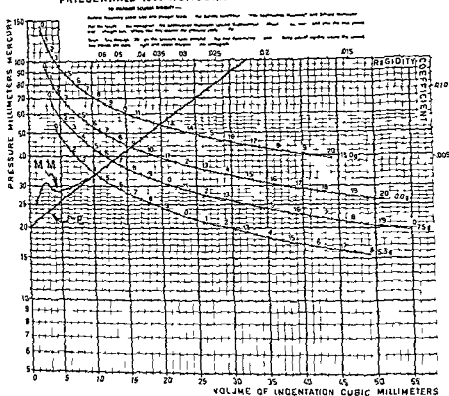


Fig 3

Mackay Marg (M M) record (Fig 2) superimposed on ocular rigidity slope (E) This figure approximates closed manometer or clinical conditions Dip in tonometer record is found at a volume displacement of about 4 ¼ l

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The second topic concerns the applanation diameter corresponding to the dip in the Mackay Marg record when the tonometer is used in its usual function in the clinical measurement of intraocular pressure In the present study we calculate that the dip is at applanation diameter of 3 mm in agreement with the findings of Stepanik (1970) At the dip in the tonometer record we calculated that actual intraocular pressure is about 8 mm higher than steady state pressure (The earlier study (Moses 1967) found the pressure 6 7 mm above uninstrumented pressure by direct measurement.)

The main point to be drawn from these experiments is that the calibration of the Mackay Marg tonometer must be related to its use If the tonometer is to be

used for constant pressure tonography it must be calibrated under constant pressure conditions If the tonometer is to be used for the clinical measurement of intraocular pressure the calibration should be conducted under closed manometer conditions and the dip in the record should be related to uninstrumented pressure

Summary

During progressive applanation with the Mackay Marg tonometer force on the tonometer plunger due to corneal distortion rapidly reaches a peak and slowly decreases until a relatively large area of cornea is flattened In tonography the area of applanation must be sufficiently large that the corneal force on the tonometer plunger is constant In tonometry the dip in the plunger displacement curve from which intraocular pressure is derived occurs at a smaller applanation

It is suggested that for tonography the tonometer calibration should be based on an open manometer system whereas for tonometry a closed manometer system should be employed

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From the Department of Ophthalmology
New York Medical College
Center for Chronic Disease Bird S Coler Hospital
Welfare Island New York New York 1001,

VOLUMETRIC STUDIES OF OPHTHALMIC ARTERY PERFUSION PRESSURE AND OCULAR RIGIDITY

BY

MICHAEL BLUMENTHAL, MILTON BEST MILES A GALIN
& NORMAN WALD

Although Friedenwald postulated a constant ocular pressure volume relationship over a wide range of intraocular pressures (1937) a number of studies have indicated the variability of this relationship (Perkins & Gloster 1957 Macri et al 195, Ytteborg 1960 Eisenlohr & Langham 1962) One component of this variable relationship may be due to alterations that occur in scleral elasticity as the tension in the ocular coats is changed with alterations in intraocular pressure (Gloster Perkins & Pommier 1957) In addition changes in intraocular blood volume at different intraocular pressures may play an important role in the *pressure volume relationship* (Ytteborg 1960) Attempts to study the effect of ocular blood volume on this relationship however have yielded inconsistent results perhaps because inadequate attention was paid to the measurements of perfusion pressure in the ocular vascular bed (Ytteborg 1960 Eisenlohr & Langham 196? Pollack & Becker 1961 Best Pola & Galin 1969)

Previous studies from this laboratory using manometric techniques indicated that there is an inverse relationship between ocular rigidity and ophthalmic artery perfusion pressures between 40 and 100 mm Hg (Blumental Best & Galin 19 0) Although ocular volume changes in this study were induced with a to

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used for constant pressure tonography it must be calibrated under constant pressure conditions If the tonometer is to be used for the clinical measurement of intraocular pressure the calibration should be conducted under closed manometer conditions and the dip in the record should be related to uninstrumented pressure

Summary

During progressive applanation with the Mackay Marg tonometer force on the tonometer plunger due to corneal distortion rapidly reaches a peak and slowly decreases until a relatively large area of cornea is flattened In tonography the area of applanation must be sufficiently large that the corneal force on the tonometer plunger is constant In tonometry the dip in the plunger displacement curve from which intraocular pressure is derived occurs at a smaller applanation

It is suggested that for tonography the tonometer calibration should be based on an open manometer system whereas for tonometry a closed manometer system should be employed

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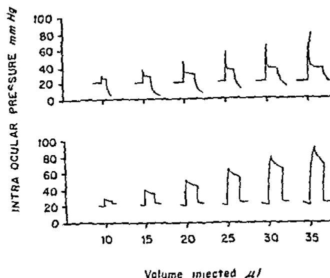


Fig 2
Intraocular pressure changes after anterior chamber injection at ophthalmic artery perfusion pressures of zero (lower trace) and 90 mm Hg (upper trace)

pressure transducer placed between the ophthalmic artery cannula and the per fusing reservoir

Pres ure volume curves for each eye were constructed from data obtained by rapidly injecting 5 to 50 ›l of lactated Ringer s solution into the anterior chamber in increments of 5 µl Each injection was performed at a baseline intra ocular pressure (P) of 20 mm Hg and the resulting intraocular pressure (P_t) was *recorded on the dynograph Just prior to injecting the lactated Ringer s solution* the open system was converted to a closed one by turning the stopcock The linear and semi logarithmic *pressure volume relationships for each eye were* plotted at ophthalmic artery perfusion pressures of 0 20 30 40 50 ›0 and 90 mm Hg Ocular rigidity was determined at each ophthalmic artery perfusion pressure from the slope of the semi logarithmic plot

Results

Fig is a typical record of *intraocular pressure* changes after injections of 5 to 0 l of lactated Ringer s solution into the anterior chamber at ophthalmic artery perfusion pressures of zero (lower trace) and 90 *mm Hg (upper trace)* l was 0 mm Hg in all cases For each volume of injection the resulting P_t

nometer and were subject to the errors involved in applying human calibration tables to the cat eye the relative changes in ocular rigidity were significant In order to avoid calibration errors the present study was undertaken to evaluate the effect of ophthalmic artery perfusion pressure on the ocular pressure volume relationship using volumetric techniques

Material and Methods

Adult cats weighing 3 to 5 kg were sacrificed with intravenous pentobarbital sodium after anticoagulation had ben effected with 2 000 units of intravenous heparin sodium The eyes were enucleated and the ophthalmic artery cannulated with PE 50 polyethylene tubing as described previously (Best et al 1969) The eye was positioned in a styrofoam socket and the anterior chamber was cannulated at the limbus both with a 23 gauge needle connected to a saline reservoir and with a 25 gauge needle attached to a 50 μl graduated microsyringe (Fig 1) Intraocular pressure was controlled with the saline reservoir and was monitored with a transducer and recorder Ophthalmic artery perfusion pressure was controlled with a reservoir of lactated Ringer s solution and was monitored with a

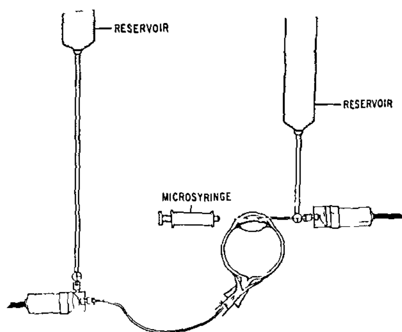


Fig 1
Schematic diagram of apparatus used to perfuse the ophthalmic artery and measure ocular pressure volume relationship

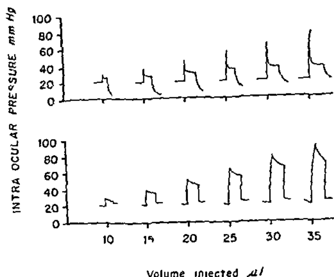


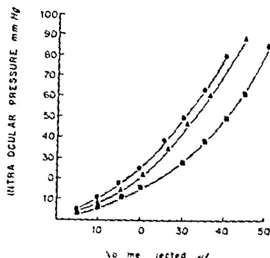
Fig 9
Intraocular pressure changes after anterior chamber injection at ophthalmic artery perfusion pressures of zero (lower trace) and 90 mm Hg (upper trace)

pressure transducer placed between the ophthalmic artery cannula and the perfusing reservoir

Pres ure volume curves for each eye were constructed from data obtained by rapidly injecting 5 to 50 µl of lactated Ringer s solution into the anterior chamber in increments of 5 µl Each injection was performed at a baseline intra ocular pressure (P) of 20 mm Hg and the resulting intraocular pressure (P_t) was *recorded on the dynograph Just prior to injecting the lactated Ringer s solution* the open system was converted to a closed one by turning the stopcock The linear and semi logarithmic pressure volume relationships for each eye were plotted at ophthalmic artery perfusion pressures of 0 20 30 40 50 70 and 90 mm Hg Ocular rigidity was determined at each ophthalmic artery perfusion pressure from the slope of the semi logarithmic plot

Results

Fig is a typical record of intraocular pressure changes after injections of 5 to 0 l *of lactated Ringer s solution* into the anterior chamber at ophthalmic artery perfusion pressures of zero (lower trace) and 90 mm Hg (upper trace) was 0 mm Hg in all cases For each volume of injection the resulting P_t



Pressure volume relationship of an eye at ophthalmic artery perfusion pressure of zero (●) 40 (▲) and 70 mm Hg (■)

value was progressively less and the slope of intraocular pressure decline from the resulting P_t value progressively steeper as ophthalmic artery perfusion pressure was raised to 90 mm Hg

From this type of data the pressure volume relationship was plotted (Fig 3) at ophthalmic artery perfusion pressures of 0 40 and 70 mm Hg Although the shapes of the curves are similar a shift to the right occurs as ophthalmic artery perfusion pressure is increased Fig 4 shows similar data plotted semi logarithmically

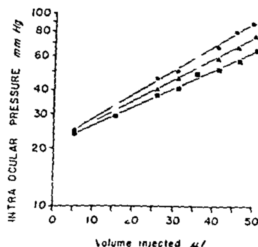


Fig 4
Semilogarithmic plot of pressure volume relationship of an eye at ophthalmic artery perfusion pressures of zero (●) 50 (▲) and 90 mm Hg (■)

Table I

Effective perfusion pressure	No of eyes	Ocular rigidity ± S D	P
0	23	0 0139 ± 0 0012	
10	17	0 0127 ± 0 0012	0 05
20	11	0 0119 ± 0 00133	0 001
30	18	0 0109 ± 0 00142	0 001
0	17	0 0101 ± 0 00129	0 001

Perfusion pressure in ophthalmic artery minus intraocular pressure

† Paired t test comparing zero ophthalmic artery perfusion pressure to each effective perfusion pressure

° Atmospheric pressure

Ocular rigidities at each ophthalmic artery perfusion pressure studied are shown in Table I which includes a statistical analysis of the results The results indicate that there is a gradual increase in ocular rigidity as perfusion pressure in the ophthalmic artery is reduced The changes in ocular rigidity are statisti cally significant using the paired t test

Discussion

A previous study using the manometric method for determining ocular rigidity indicated that blood expulsion from the eye during tonometry is of importance in measuring intraocular pressure and ocular rigidity (Blumenthal Best & Galin 1970) The present study using a volumetric technique confirms this finding and shows the volume of fluid expelled from the vascular compartment is di rectly related to the ophthalmic artery perfusion pressure The kinetics of fluid expulsion from the eye after injection of lactated Ringer s solution into the anterior chamber is represented in Fig 2 where intraocular pressure change is plotted for ophthalmic artery perfusion pressures of zero and 90 mm Hg Injec tions of fluid in the former case cause an intraocular pressure increase which is followed by a small but rapid decline in intraocular pressure to a new level This rapid decline in intraocular pressure is more apparent with increasing in jection volumes and is probably related to the viscoelastic properties of the sclera (McEwen 1961) The *rapid decline is followed by a slower continuous* decline in intraocular pressure that is apparently due to outflow of fluid from

the anterior chamber angle After anterior chamber injection in the eye whose ophthalmic artery was perfused at 90 mm Hg however the rapid decline in intraocular pressure from its new level was very much more marked and was most likely due to rapid expulsion of fluid from the intraocular vascular compartment through the venous outflow channels as well as to scleral viscoelasticity

At higher ophthalmic artery perfusion pressures therefore more fluid is available in the vascular bed for expulsion at the increased intraocular pressure, resulting in the very prominent peaking of the biphasic intraocular pressure decay curve Injections of the same amount of fluid into the anterior chamber at different ophthalmic artery perfusion pressures consequently are immediately buffered by discharge from the vascular bed resulting in smaller increases in intraocular pressure at the higher ophthalmic artery perfusion pressures as compared to the lower ones This explains the findings of a shift to the right of the pressure volume curve as ophthalmic artery perfusion pressure is increased

When the ophthalmic artery perfusion pressure was increased to only 10 mm Hg above intraocular pressure the shift in the pressure volume relationship did not occur using zero ophthalmic artery perfusion pressure as the comparative baseline This is probably due to the fact that an ophthalmic artery perfusion pressure of only 10 mm Hg greater than intraocular pressure is unable to prevent critical closure of intraocular vessels from occurring (Best et al 1969) The phenomenon of critical closure occurs in many vascular beds as transmural pressure approaches zero and perhaps provides the explanation for several observed ocular vascular phenomena (Blumenthal et al 1970) Under these circumstances filling of the intraocular vascular bed does not occur When ophthalmic artery perfusion pressure exceeded intraocular pressure by 30 mm Hg or more however the anticipated alterations in the pressure volume relationship were detected (Table I)

Summary

The pressure volume relationship of enucleated cat eyes was studied by a volumetric technique while the perfusion pressure of the intraocular vascular bed was controlled by cannulating the ophthalmic artery The intraocular pressure changes induced by intracameral injection of lactated Ringer s solution were significantly reduced as ophthalmic artery perfusion presure was increased This probably results from the rapid reduction of the intraocular vascular compartment through the venous outflow channels at higher ophthalmic artery perfusion pressures The results indicate an inverse relationship between ocular rigidity and ophthalmic artery perfusion pressure

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Moreau P G & J Haut Cryo Ophthalmologie. In collaboration with R. Alfieri M Brihaye P Payrau Y Pouliquen, D Simatos & P Solé Report to the Societe Française d Ophthalmologie 1971 Masson, Paris 746 pages

As usual this year s report on cryo ophthalmology to the French Ophthalmological Society is a very elaborate complete, and well disposed presentation which reflects the explosive introduction of cryo intervention in ophthalmology The physical pheno menons the instrumentation and the reactions of the different oclar tissues to freezing are properly described The clinical applications comprise cataract extraction choreo retinal affections glaucoma conjunctival and corneal diseases tumors and intervention in the vitreous Cold storage of ocular tissues is also described

P Brændstrup

Glaukom Probleme Report of the 43rd annual meeting of the Society of Rhein Main Ophthalmologists 19,0 W Straub edit Bucherei des Augenarztes Beiheft 56 1971 der Klinischen Monatsblatter fur Augenheilkunde Ferdinand Erke Stutt gart 1971 81 pages

This report – written in German – contains six wise and informative lectures on glau coma problems given in a session for practising ophthalmologists by prominent col leagues It can be well recommended

The lectures are *J W Rohen* Morphology of the chamber angle and its relation to glaucoma problems *E Aulhorn* Clinical testing of the visual field in glaucoma *J Draeger* Tonometry and tonography *W Leydhecker* Failures in medical treatment of glaucoma *H Saulter* Clinical morphology of the chamber angle *R Witmer* Indi cations and techn que of glaucoma operations

P Brændstrup

C Offret & C Haye Tumeures de l oeil et des annexes oculaires Masson et Cie Paris 19,1 608 pages 377 figures format 17 × 25 cm Price 190 F

This a very didact c and practical book which does not aim at an encyclopedic pres entation but is written for the student the practising ophthalmologist and must be very aluable for a cancerologist as well It may be well recommended

Clini al manifestations evolution and treatment are very precisely described and the llustrations are well chosen and informative. Histology is restricted to a necessary minimum

The book is d vided in the following sections Tumors of the eyelids conjuctiva corn a and sclerotic uvea retina optic nerve, orbit and lacrymal apparatus

A special s ct on deals with the compl cations of irradiational treatment

B bl gra hy foll ws each chapter and the book contains an author and a subject index

P B andstrup

F Hervouet Atlas pratique de la chirurgie du strabisme Indications operatoires, Technique chirurgicale Masson et Cie Paris 1970 418 pages Price Fr 200 00

This book appeals to the practising ophthalmologist who has had limited experience in the field of strabismic surgery The author has performed more than 4000 strabismic operations and reports in a refreshing and inspiring way his own indications and technique

As is implied in the title the essential part of the book is pictures exclusively photographs of which 25 000 have been taken to fill this book (The photograph is a document incomparable) The photographs are extremely illustrative and express more than many descriptions with prism measurements etc

The operative technique is gone into in detail in pictures In the dosage of the surgery great emphasis is placed amongst other things on the forced duction test in universal anaesthesia The language problems are not great even for those with a limited knowledge of French because of the many pictures

The book can be recommended as an inspiring and easily accessible photographic atlas for eye specialists who wish to have practical knowledge about strabismic operations

Jess Olsen

The *First International Surgical Eye Symposium* will be held in Bologna (Italy) from April 23rd to 24th 1972 Refined surgical techniques in the management of chamber angle for glaucoma congenital and senile cataracts corneal lesions prostheokerato plasties and plastic surgery of the lids and orbit will be demonstrated live by a group of world renowned surgeons Operative sessions will be televised Translations in various languages Papers related to the above subjects and the recent advances in orbitography ultrasonography fluorescine angiography etc will be presented by a distinguished panel Registration fee $ 100 00 (U S)

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IVth International Ergophthalmological Symposium

In connection with the IVth Congress of the Societas Ophthalmologica Europaea, the International Association of Ergophthalmology is planning to hold the IVth Symposium on Ergophthalmological Problems in Budapest on *April 16th* at *9 30* a m

Themes which are foreseen 1 *Efficiency* demands of the visual organ of workers with and without protective goggles 2 *Illumination* for working 3 *Rehabilitation* of visually handicapped persons

Applications for taking part and for scientific reports should be sent as soon as possible to the General Secretary of the Association Professor Dr Enrique López Quinones Leibnitz 47 403 Mexico 5 D F Mexico – or to the secretary for Europe Dr L Toppel Augenklinik rechts der Isar Der Technischen Universitat Munchen D 8000 Munchen 80 Ismaninger Strasse 22

H J Merte Munchen
President of the International
Association of Ergophthalmology

ACTA OPHTHALMOLOGICA VOL. 49 1971

*From the Departments of Ophthalmology and Biophysics
Medical College of Virginia
Health Sciences Division Virginia Commonwealth University
Richmond Virginia*

EFFECTS OF ACUTE AND PROTRACTED IONIZING RADIATION ON THE RABBIT LENS

BY

W J GEERAETS W T HAM H A. MUELLER R C WILLIAMS & S F CLEARY

PART I

ACUTE X RAY AND PROTON IRRADIATIONS

Introduction

With the advancement of manned space exploration potentially hazardous exposure levels to ionizing radiation deriving from the continuous fields of the van Allen belt to less predictable exposures from solar flares have been of concern While the former can be avoided to some degree by selected orbital flight patterns solar flares may present some problems Since the eye is a superficially located organ and its lens is a relatively sensitive biological structure responding to ionizing radiation with characteristic changes easily observable under *in vivo* biomicroscopy it lends itself particularly well to studying effects of selected dose and energy levels To accomplish this goal the following investigations were conducted

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Received March 6 19 1

Method

Dutch rabbits were used throughout this investigation for various reasons (1) A study of effects of acute X-ray exposures had been completed previously (Geeraets et al 1965 Ham et al 1967) using the same species (2) Handling biomicroscopic examinations economic criteria, maintenance and the life span of these experimental animals made them very suitable for this investigation (Geeraets et al 1965 Ham et al 1967) All animals were carefully screened before including them in this study to avoid any lens anomalies to be incorporated in this follow up evaluation of radiation effects

Acute exposures of the Dutch rabbit lens to 1 Mev X radiation 20 Mev and 100 Mev protons were evaluated with regard to radiation dose, and to development and degree of lenticular changes with time The radiation schedules for the various exposures were 125 r X ray from a 1 Mev X ray unit – to supplement the data of previous investigations under AEC contract for acute X ray exposure at dose levels from 25 r to 1000 r (Geeraets et al 1965 Ham et al 1967) – and for the proton beam exposures two energies 20 Mev and 100 Mev were applied for a limited study of the linear energy transfer (LET) of the protons and their biological interaction with the rabbit lens The dose for the proton exposures ranged from 25 to 500 rad The physical parameters and methodology applied in this investigation were described by Cleary et al (In press)

Since the degree of lenticular changes after exposure to ionizing radiation depends on varions physical properties these aspects were rigidly controlled within the experimental design with regard to total energy applied radiation source and intensity and radiation profile or distribution The two LET values were selected arbitrarily and based more on the availability than on theories of radiobiological effectiveness Throughout the studies collimation of the exposure beams was assured thus eliminating side effects including those not necessarily interfering with local lens pathology

Nine rabbits were exposured to a 1 Mev X ray beam and a dose of 125 r to supplement previous data as well as to study the repeatability of previously obtained data For acute proton irradiations at 20 and 100 Mev energies a total of 30 rabbits was used Selected radiation doses given at the 160 Harvard University Synchrocyclotron were 25 50 100 and 250 rad thus allowing 3 animals for each dose and energy level Six additional rabbits were kept as controls for both energy levels and were handled in a similar fashion as the experimental animals with the exception of radiation exposure Another 15 rabbits were exposed at the 600 Mev Synchrocyclotron of the National Aeronautics and Space Administration Space Radiation Effects Laboratory (SREL) Three groups of 5 animals each were exposed to an acute dose of 25 125 and 500 rad/100 Mev respectively In all experimental animals only one eye was irradiated with the fellow eye serving as a control beside the non exposed control group

No anesthesia was used during radiation exposure to eliminate possible unknown artifacts During exposure and subsequent biomicroscopic examinations immobilization of the animals was achieved by merely wrapping the rabbit in a towel If done correctly this way of immobilization is of no distress to the animal and assures proper handling alignment during exposure, biomicroscopic examination and elimination of any drug effects on metabolic actions which may remotely be claimed as a possible factor interfering with normal lens development and/or changes and at the same time it reduces the chance of mortality due to anesthesia In spite of the acquired exposure technique the positioning of the rabbit eye in alignment with the exposure beam was monitored at all times over a closed circuit TV system and was adjusted in cases where this was required

With the relatively small sampling of the various groups of radiation doses it admittedly remains difficult to come to final conclusions Therefore the presented findings can only be regarded as giving a certain direction in which further research efforts should be pursued

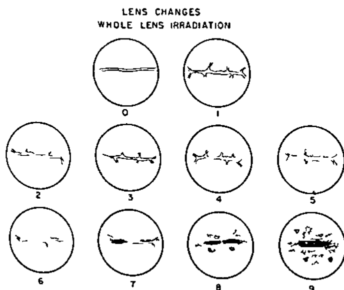


Fig I 1

Schematic drawing of observed lens changes after whole lens irradiation. The number underneath each drawing represents the grade of lens changes (see text) 0 represents the initial appearance of all lenses used in the study 1 shows changes which occur with age through 9 show lens changes in order of increasing severity which developed in irradiated lenses during the observation period

However, in spite of the relatively small sampling of the various parameters of this pilot study it has given valuable information that radiation dose LET and degree of lens changes are interlinked and dependent on each other when biological interferences are considered

During the first 6 months after radiation exposure biomicroscopic examination of the rabbit lens was performed twice monthly thereafter every month up to one year and every three months for a total of 3 to 4 years Classification of degree of lens changes with age or as a result of radiation exposure were equal to those reported previously (Geeraets et al 1965) with grades ranging from 0 to 9 It should be repeated here that this grading is based on subjective biomicroscopic findings by one of the authors (W J G) Lens changes were recorded by drawing without previous records being available to the examiner at any time throughout the period of investigation Drawings were preferred over photographic documentation for greater accuracy

The term "cataract has purposely been avoided in this text because of the variation in definition by various investigators and/or clinicans It should therefore be understood that the most minute changes described can be regarded as a sensitive biological dosimeter" in radiation damage to the lens though they certainly would not affect vision

A brief description of the various degrees of lens changes according to the selected grade of severity follows (see also Fig 1–1)

Grade 0 Double contoured white horizontal suture lines in posterior subcapsular areas fading into a fine haze towards the center of the lens No coarse or medium sized dots and no more than five fine dots present

Grade 1 Same as 0 but moderate number of fine dust like dots and a few larger dots white and sharply outlined in the posterior cortex along both sides of the suture lines The suture line shows branching mainly on the two ends but also along the entire course Less than five coarse dots along the posterior suture lines

Grade 2 Any features described under 0 or 1 but in addition one or two white linear opacities near the suture lines and oriented in the direction of the individual lens fibers in that particular area Coarse dots up to 10

Grade 3 Same as 2 but up to 30 linear opacities and or increase in larger dots

Grade 4 The suture line is branched but shows in addition interruptions in continuity besides the features described in 3 and up to 50 and above coarse opacities

Grade 5 Increasing number of hard white dots and linear opacities Beginning of a haziness in the posterior cortex

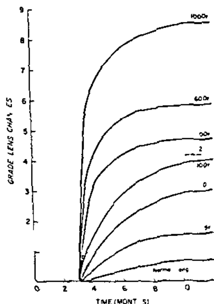


Fig 1 9
Graph representing development of lens changes according to grades of severity illus trated in Fig 1 1 after radiation exposure of various doses from a 1 Mev X ray unit. Each curve represents the mean value for the individual dose groups

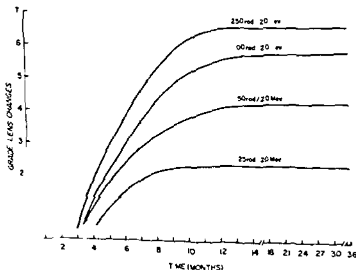


Fig 1 3
O set and progress on of lens changes after single exposure to various doses of a °0 Mev proton beam (Harvard University Synchrocyclotron)

Grade 6 Same as in 5 but more pronounced haziness Suture line still double contoured with branching

Grade 7 Suture lines in some areas thickened and dense white but partially still double contoured Haziness in posterior cortex increased with radiating pattern particularly in central portion of the posterior cortex

Grade 8 Double contoured suture lines have disappeared leaving only dense thick white fragments in posterior cortex within the veil like haziness and numerous heavy dot like opacities and occasional vacuoles There were no changes in the lens periphery (biomicroscopically) Few dot like opacities might be located in anterior cortex

Grade 9 Same as in 8 however all changes are somewhat more anterior with regard to the posterior capsule The earlier suture lines appear to have contracted into a thick rock like mass with a rough cratered surface The veil like haziness extends from this mass in a somewhat posterior direction toward the periphery

Results

X Rays

Lens changes for acute X ray irradiation of dose levels 25 50 100 200 600 and 1000 r were described previously (Geeraets et al 1965) The control group in this study exposed to a single X ray dose of 125 r to verify former observations shows a mean onset of lens changes about 4 months after exposure with a progression of lens opacities at a similar rate for this dose level as described in the earlier communication A plateau after which no further increase in lens changes could be observed biomicroscopically was reached at approximately 12 months after irradiation and the degree was classified between grade 4 and 4 5 which corresponds also with the earlier findings Total observation time was 3 years over which no further changes took place beyond those present at 12 months post exposure (Fig 1 2)

PROTONS (20 Mev energy) – Harvard University Synchrocyclotron

For the four dose levels (25 50 100 and 250 rad) first lens changes were noted between the 3rd and 5th month post irradiation Although for the various doses lens changes did not progress or regress after 12 months post irradiation the progression within the first year was somewhat slower in comparison with those seen after X ray exposure At higher dose levels it was noted that the final degree of lens changes was more pronounced after proton irradiation than after

Table 1 1

The numbers represent the grade of lens changes for selected examination dates and show *variations within groups* which had been exposed to various dose levels of a 20 Mev proton beam (Harvard University Synchrocyclotron) 0 1 represents a normal range of lens variations most likely not attributable to irradiation. + = Experimental *animal expired* No further lens changes beyond the tabulated *observation time were* noted and are therefore *omitted*

abbit #	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15–36 months
	20 Mev proton beam															
	Single dose – Examinations once monthly post exposure															
	[illegible]0 rad															
83	0-1	0-1	0 1	0-1	2	3	3	4+	5	5	6	6	6	6+	6+	
86	0 1	0 1	0-1	0-1	2	3	4	5	5+	6	6+	7	7	7	7	No further change
87	0-1	0 1	0-1	0-1	2	3	3+	4+	5	6	6	6+	+			
	100 rad															
81	0-1	0-1	0-1	0-1	0-1	2	2+	3	4	4+	+					
85	0-1	0-1	+													No further change
93	0-1	0-1	0 1	0 1	0-1	2	3	4	4+	5	5	5+	5+	6–	6–	
	50 rad															
8[illegible]	0-1	0-1	0-1	0-1	0-1	0-1	2	+								
97	0-1	0-1	0-1	0-1	0-1	2	2	2+	3	3+	4–	4	4	4	4	No further change
96	0-1	0-1	0-1	0-1	0-1	2	2+	3	3+	4	4	4	4	4+	4+	
	[illegible] rad															
9[illegible]	0-1	0-1	0-1	0-1	0-1	0-1	0-1	2	2	2	2+	2+	2+	2+	2+	
94	0-1	0-1	0-1	0-1	0-1	0-1	2	2	2	2+	2+	2+	2+	2+	2+	No further change
111	0 1	0 1	0-1	0-1	0-1	0-1	+									

1 Mev X radiation At lower levels this was not as obvious (Fig 1 3) The range of lens changes within each group for *individual* examination times is presented in table 1–1

PROTONS (100 Mev energy) – Harvard University Synchrocyclotron

For equal dose levels as described for the 20 Mev proton beam onset progression of lens changes and final plateau about 12 months post exposure were similar *in this experimental* group with one exception that final degree in

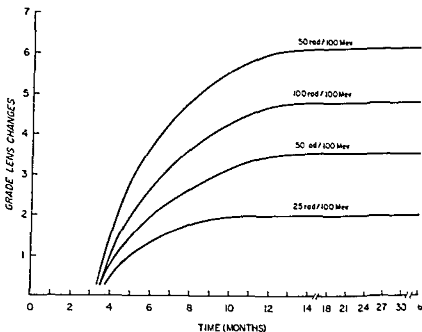


Fig 1 4

Onset and progression of lens changes after single exposure to various doses of a 100 Mev proton beam (Harvard University Synchrocyclotron)

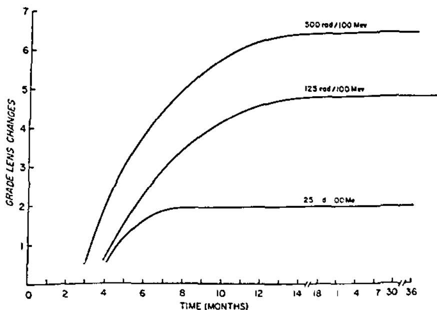


Fig 1 5

Onset and progression of lens changes after single exposure to various doses of a 100 Mev proton beam (SREL Synchrocyclotron)

severity of lens changes was slightly but significantly less pronounced (Fig 1 4) See Table 1 1 for range in degree of lens changes for individual examination times and various dose groups

For dose levels 25 125 and 500 rad (SREL – Synchrocyclotron) it was noted that for the 500 rad exposure progression and final degree of lens opacities were almost equal to the above group which had received 250 rad/100 Mev exposures The only explanation for this observation is thought to be due to the fact that the rabbits in this group were approximately one or two months older at the time of exposure than the group which received 250 rad (Fig 1 5) Range of lens changes is given in Table 1 2

Conclusions

1 Exposure of rabbit lenses to the higher LET 20 Mev proton beam results in more pronounced lens changes than the ones exposed to a lower LET 100 Mev proton irradiation at identical dose levels (25 50 100 250 rad) Figs 1 3 1 4 1 6

2 The effect of proton irradiation for the two energy levels (20 Mev 100 Mev) in producing lens changes is significantly greater than the effect caused by 1 Mev X radiation This is more pronounced for higher dose levels

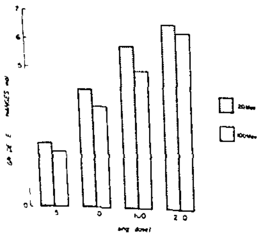


Fig 1-6
Comparison of final grades of lens changes for various dose levels and two proton beam energies.

Table 1 2

See caption of Table 1 1 with the exception that the proton beam energy was 100 Mev

Rabbit #	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15–36 months
100 Mev proton beam																
Single dose – Examinations once monthly post exposure																
250 rad																
100	0–1	0–1	0–1	0–1	2	3	3	4	+							
107	0–1	0–1	0–1	0–1	0–1	2	3	4	4	5	5+	6	6	6	6	No further changes
110	0–1	0–1	0–1	0–1	2	3	4	5	5	5+	6	6	6+	6+	6+	
100 rad																
97	0–1	0–1	0–1	0–1	0–1	2	3	3	4	4	4	4	4+	5	5	
101	0–1	0–1	0–1	0–1	0–1	2	2	3	3	4	4	4+	5–	5–	5–	No further changes
104	0–1	0–1	0–1	0–1	2	2	3	3+	4	4	5	5	5	5	5	
50 rad																
99	0–1	0–1	0–1	0–1	0–1	0–1	2	2	2+	3	3+	4	4	4	4	
102	0–1	0–1	0–1	0–1	0–1	2	+									No further changes
103	0–1	0–1	0–1	0–1	0–1	0–1	2	3	3	3	3	3	3	3	3	
25 rad																
88	0–1	0–1	0–1	0–1	0–1	0–1	0–1	0–1	2	2	2	2	2	2	2	
89	0–1	0–1	0–1	0–1	0–1	2	2	2	2	2	2	2	2	2	2	No further changes
90	0–1	0–1	0–1	0–1	0–1	0–1	2	2	2	2	2	2	2	2	2	

3 The biomicroscopic appearance of lens changes produced either by proton irradiation or X ray is characteristic but similar for the two modes of exposure This may indicate that the pathogenesis is the same for the two types of irradiation

4 The onset of lens changes produced by irradiation to a proton beam was approximately equal to that after X ray exposure Progression of lens changes however appeared slower for the former A plateau after which no further lens changes occurred was reached for both types of irradiation about 12 months post exposure

Table 1 3

ee caption of Table 1 2 with the exception that irradiation was performed at the SREL – Synchrocyclotron and that *different dose levels were used*

	100 Mev proton beam															
	Single dose – Examinations once monthly post exposure															
#	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15–24 months
	500 rad															
	0–1	0–1	0–1	0–1	2	3	4	5	+							
	0–1	0–1	0–1	0–1	2	3	4	4+	5	5	6	6	6	7	7	
	0–1	0–1	0–1	0–1	0–1	2	3	4	5	5	5	6	6	6	6	No further changes
	0–1	0–1	0–1	0–1	2	3	4	5	5	6	6	6	6	6	6	
	0–1	0–1	0–1	0–1	2	3	4	5	5+	6	6	6+	7	7	7	
	125 rad															
	0–1	0–1	0–1	0–1	0–1	0–1	2	3	3	4	4	4	4	4+	4+	
	0–1	0–1	0–1	0–1	0–1	2	3	3	+							
	0–1	0 1	0–1	0–1	0–1	0–1	2	3	4	4	5	5	5	5	5	No further changes
	0–1	0–1	0–1	0–1	0–1	2	2	3	3+	4	4	4+	5	5	5	
	0–1	0–1	0–1	0–1	0–1	+										
	25 rad															
	0–1	0–1	0–1	0–1	0–1	0–1	2	2	2	2	2	2	2	2	2	
	0–1	0–1	0–1	0–1	0–1	0–1	2	2	2	2	2	2	2	2	2	
	0–1	0–1	0–1	0–1	0–1	2	2	2	2	2	2	2	2	2	2	No further changes
	0–1	0–1	0–1	0–1	0–1	0–1	0–1	0–1	2	2	2	2+	+			
	0–1	0–1	0–1	0–1	0–1	0–1	0–1	2	2	2	2	2	2	2	2	

PART II

FRACTIONATED X-RAY AND PROTON IRRADIATION

Protracted irradiation at dose levels applied in this investigation was selected to study accumulative effects on the lens as a laboratory simulation of possible exposures of astronauts on prolonged space missions.

Method

The physical parameters of this part of the investigation were identical to the ones described in Part I of this investigation. Classification of lens changes were also equal to those discussed in Part I and covered in greater detail in a previous publication (Geeraets et al. 1965). The Dutch rabbits used in this part of the experiment were screened for absence of any lens anomalies prior to the first radiation exposure. They were re-examined twice monthly for one year, once monthly for the second year and every three months thereafter for a total of three to four years. Any lens changes were recorded by detailed drawings and these drawings were graded after completion of the study. The degree of severity of lens changes was then plotted as the mean for each energy and dose group. The range for each group is presented in Tables 2.1 – 2.4.

Various exposure schedules for X-ray irradiation were used and are tabulated as follows:

Fractionated X-ray irradiation

		No. of rabbits
19.3 r	1 × weekly for 13 weeks (total 250 r)	12
25 r	3 × weekly for 13 weeks (total 1000 r)	5
25 r	1 × monthly for 10 months (total 250 r)	6
50 r	1 × monthly for 10 months (total 500 r)	9
100 r	1 × monthly for 10 months (total 1000 r)	9

For fractionated exposure to a 30 Mev and 100 Mev proton beam the doses were 5, 12.5, 25 and 50 rad given once monthly for 10 consecutive months thus totalling 50, 125, 250 and 500 rad. Each group contained six or seven rabbits. Only one eye was exposed to the proton beam. The irradiation was performed at the 600 Mev Synchrocyclotron, National Aeronautics and Space Administration Space Radiation Effects Laboratory (SREL).

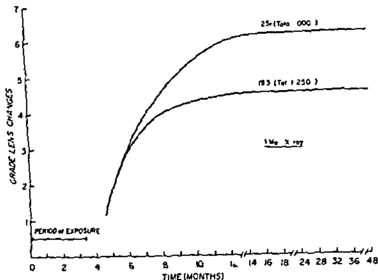


Fig 2 1

Graph representing development of lens changes after protracted irradiation to two individual doses – 19 3 and 25 r – from a 1 Mev X ray unit – over a 13 weeks irradiation time totalling 250 and 1000 r respectively

Results

X-ray

Both groups of rabbits exposed over a period of 13 weeks to individual doses of 19 3 and 25 r resulting in a total dose of 250 and 1000 r respectively showed first biomicroscopic minimal lens changes approximately 4 months after the first exposure This interval after the first exposure and the observable lens changes correspond to observations made previously after single X ray exposure of same dose levels Thus the additional exposures in these two groups of protracted irradiation did not shorten the latent period between first exposure and first *in vivo* detectable lens changes (Fig 2 1*)

The initial slope of the two curves representing the progress in lens opacities for the two dose levels were identical up to approximately 6 months post initial exposure The degree of lens changes corresponded at that time to a grade 3 of the grading system applied in previous investigations (Cleary et al in press Geeraets et al 1965) After this time progression of lens changes deviated for

Classification and grading of lens changes were discussed in detail in Part I of this report Figures and tables are indicated by two numbers the first giving reference to the individual part of the study the second number represents the illustration or table in that part

PART II

FRACTIONATED X-RAY AND PROTON IRRADIATION

Protracted irradiation at dose levels applied in this investigation was selected to study accumulative effects on the lens as a laboratory simulation of possible exposures of astronauts on prolonged space missions

Method

The physical parameters of this part of the investigation were identical to the ones described in Part I of this investigation Classification of lens changes were also equal to those discussed in Part I and covered in greater detail in a previous publication (Geeraets et al 1965) The Dutch rabbits used in this part of the experiment were screened for absence of any lens anomalies prior to the first radiation exposure They were re examined twice monthly for one year once monthly for the second year and every three months thereafter for a total of three to four years Any lens changes were recorded by detailed drawings and these drawings were graded after completion of the study The degree of severity of lens changes was then plotted as the mean for each energy and dose group The range for each group is presented in Tables 2 1 – 2 4

Various exposure schedules for X ray irradiation were used and are tabulated as follows

Fractionated X ray irradiation

		No of rabbits
19 3 r	1 × weekly for 13 weeks (total 250 r)	12
25 r	3 × weekly for 13 weeks (total 1000 r)	5
25 r	1 × monthly for 10 months (total 250 r)	6
50 r	1 × monthly for 10 months (total 500 r)	9
100 r	1 × monthly for 10 months (total 1000 r)	9

For fractionated exposure to a 30 Mev and 100 Mev proton beam the doses were 5 12 5 25 and 50 rad given once monthly for 10 consecutive months thus totalling 50 125 250 and 500 rad Each group contained six or seven rabbits Only one eye was exposed to the proton beam The irradiation was performed at the 600 Mev Synchrocyclotron National Aeronautics and Space Administration Space Radiation Effects Laboratory (SREL)

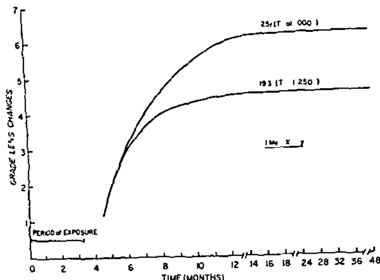


Fig 2 1

Graph representing development of lens charges after protracted irradiation to two individual doses – 19 3 and 25 r – from a 1 Mev X ray unit – over a 13 weeks irradiation time totalling 250 and 1000 r respectively

Results

X-ray

Both groups of rabbits exposed over a period of 13 weeks to individual doses of 19 3 and ²5 r resulting in a total dose of 250 and 1000 r respectively showed first biomicroscopic minimal lens changes approximately 4 months after the first exposure This interval after the first exposure and the observable lens changes *correspond to observations made previously after single X ray exposure of same* dose levels Thus the additional exposures in these two groups of protracted irradiation did not shorten the latent period between first exposure and first *in vivo* detectable lens changes (Fig 2 1*)

The initial slope of the two curves representing the progress in lens opacities for the two dose levels were identical *up to approximately 6 months post initial* exposure *The degree of lens changes corresponded at that time to a grade 3 of* the grading system applied in previous investigations (Cleary et al in press Geeraets et al 1965)* After this time progression of lens changes deviated for

Class f cation and grading of lens changes were *discussed in detail in Part I of this* report Figur and tables are indicated by two numbers the first giving reference to the nd vidual part of the study the second number represents the illustration or table n that part

Table 2-1

The numbers represent the grade of lens changes and variations for each given examination time within the various dose groups exposed to a 1 Mev X ray unit Examinations are recorded in this table *once monthly after first* radiation exposure Grading according to the system described in detail in Part I of this series

1 Mev X ray																			
Examinations once monthly *post 1st exposure*																			
Rabbit #	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	15	16	17 – 48 months
25 r (3 × weekly for 13 weeks) – total 1000 r																			
754	0–1	0–1	0–1	0–1	0–1	0–1	+												
755	0–1	0–1	0–1	0–1	+														
756	0–1	0–1	0–1	0–1	0–1	2	3	4	5	6	6	6	6	6+	6+				
757	0–1	0–1	0–1	0–1	0–1	2	3	4	5	5	6	6	6	6	6				
758	0–1	0–1	0–1	0–1	0–1	0–1	2	4	4	5	5	+							
759	0–1	0–1	0–1	0–1	0–1	2	3	3	4	4+	5	+				No further changes			
761	0–1	0–1	0–1	0–1	0–1	2	3	4	5	5	+								
762	0–1	0–1	0–1	0–1	0–1	2	3	4	5	5	6	6	6	6+	6+				
763	0–1	0–1	0–1	0–1	0–1	2	3	4	4	5	5	5	6	6	6				
764	0–1	0–1	0–1	0–1	0–1	0–1	3	3	4	4+	5	5+	6	6	6				
19 3 r (1 × weekly for 13 weeks) – total 250 r																			
768	0–1	0–1	0–1	0–1	0–1	2	3	3	4	4	4+	4+	4+	4+	4+				
769	0–1	0–1	+																
770	0–1	0–1	0–1	0–1	0–1	2	3	4	4	4+	4+	4+	5	5	5				
771	0–1	+														No further changes			
772	0–1	0–1	0–1	0–1	0–1	2	3	3+	4	4	4	4	4	4	4				

the two dose levels though both came to a final plateau after which no further increase occurred at approximately 12 14 months post first exposure Thereafter the eyes which had received a total of 250 r over a period of 13 weeks reached a grade 4 5 and the eyes exposed to a total of 1000 r over the same time period fell in the classification of grade 6+ These values correspond to grade 5 and grade 8 5 respectively for equal total doses delivered in a single exposure The spread of data for lens changes and both dose levels at various examination times is given in Table 2 1

X-ray 25 r (once monthly × 10) total 250 r

First biomicroscopic changes were observed about four to five months after initial radiation The progression of lens changes was somewhat slower and at a lesser degree when compared to values obtained from observations accumu lated from lenses exposed to an equal single dose of 250 r A final plateau after which no further increase in lens changes occurred was reached between 18 and 20 months after first irradiation and corresponded to a grade 4 5 as a mean for this group (Fig 2 2) The range is given in Table 2 2

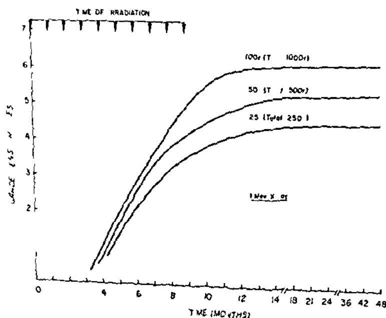


Fig 2 2

Graph representing development of lens changes after fractionated exposures to 25 50 and 100 r once monthly for 10 months from a 1 Mev X ray unit

Table 2 1

The numbers represent the *grade of lens changes* and *variations for each* given examination time within the various dose groups exposed to a 1 Mev X ray unit Examinations are recorded in this table once monthly after first radiation exposure Grading according to the system described in detail in Part I of this series

Rabbit #	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	15	16	17 – 48 months
										I Mev X ray									
Examinations once monthly post 1st exposure																			
25 r (3 × weekly for 13 weeks) – total 1000 r																			
754	*0–1*	*0–1*	*0–1*	*0–1*	*0–1*	0–1	+												
755	0–1	0–1	0–1	0–1	+														
756	0–1	0–1	0–1	0–1	0–1	2	3	4	5	6	6	6	6	6+	6+				
757	0–1	0–1	0–1	0–1	0–1	2	3	4	5	5	6	6	6	6	6				
758	0–1	0–1	0–1	0–1	0–1	0–1	2	4	4	5	5	+							
759	0–1	0–1	0–1	0–1	0–1	2	3	3	4	4+	5	+				No further changes			
761	0–1	0–1	0–1	0–1	0–1	2	3	4	5	5	+								
762	0–1	0–1	0–1	0–1	0–1	2	3	4	5	5	6	6	6	6+	6+				
763	0–1	0–1	0–1	0–1	0–1	2	3	4	4	5	5	5	6	6	6				
764	0–1	0–1	0–1	0–1	0–1	0–1	3	3	4	4+	5	5+	6	6	6				
19 3 r (1 × weekly for 13 weeks) – total 250 r																			
768	0–1	0–1	0–1	0–1	0–1	2	3	3	4	4	4+	4+	4+	4+	4+				
769	0–1	0–1	+																
770	0–1	0–1	0–1	0–1	0–1	2	3	4	4	4+	4+	4+	5	5	5				
771	0–1	+														No further changes			
772	0–1	0–1	0–1	0–1	0–1	2	3	3+	4	4	4	4	4	4	4				

the two dose levels though both came to a final plateau after which no further increase occurred at approximately 12 14 months post first exposure Thereafter the eyes which had received a total of 250 r over a period of 13 weeks reached a grade 4 5 and the eyes exposed to a total of 1000 r over the same time period fell in the classification of grade 6+ These values correspond to grade 5 and grade 8 7 respectively for equal total doses delivered in a single exposure The spread of data for lens changes and both dose levels at various examination times is given in Table 2 1

X ray 25 r (once monthly × 10) total 250 r

First biomicroscopic changes were observed about four to five months after initial radiation The progression of lens changes was somewhat slower and at a lesser degree when compared to values obtained from observations accumulated from lenses exposed to an equal single dose of 250 r A final plateau after which no further increase in lens changes occurred was reached between 18 and 20 months after first irradiation and corresponded to a grade 4 7 as a mean for this group (Fig 2 2) The range is given in Table 2 2

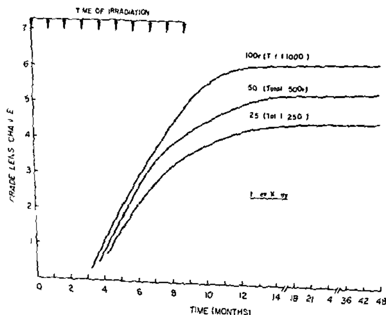


Fig 2 2

Graph representing development of lens changes after fractionated exposures to 25 50 and 100 r once monthly for 10 months from a 1 Mev X ray unit.

Table 2 2

See caption of Table 2 1

1 Mev X ray

Examination (in months) post 1st exposure

Rabbit #	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
100 r once monthly × 10																			
B 7	0–1	0–1	0–1	0–1	0–1	2	3	3	4	5	6	+							
B–8	0–1	0–1	0–1	0–1	1	2	2	2	3	4	5	5	6	6	6	6+	6+		
B–9	0–1	0–1	0–1	0–1	1	2	3	3	4+	5	5	6	6	6	6	6	6		
B–10	0–1	0–1	0–1	0–1	0–1	1	2	2	3	4+	5	5	5+	6	6	6	6		
B–11	0–1	0–1	0–1	0–1	1	2	2	+											
B–17	0–1	0–1	0–1	0–1	0–1	2	3	3	4+	5	5+	6	6+	6+	6+	6+	6+	No further changes	
B–18	0–1	0–1	0–1	0–1	1	1	2	3	4	+									
B–23	0–1	0–1	0–1	0–1	1	2	3	3	4+	5+	6	6	6	6	6	6	6		
B–25	0–1	0–1	0–1	0–1	0–1	2	3	3	4+	5+	6	6	6	6	6	6	6		
50 r once monthly × 10																			
B–13	0–1	0–1	0–1	0–1	0–1	0–1	2	3	4	4	5	5	5	5	5	5	5		
B–14	0–1	0–1	0–1	0–1	0–1	2	2	3	4	4	4	4	4	5	5	5	5		
B–15	0–1	0–1	0–1	0–1	0–1	2	3	4	+										
B–16	0–1	0–1	0–1	0–1	0–1	0–1	2	3	+										
B–26	0–1	0–1	0–1	0–1	0–1	2	3	4	4	5	5	5	5	5+	6	6	6	No further changes	
B–27	0–1	0–1	0–1	0–1	0–1	0–1	2	3	3	4	4	5	5	5	5	5	5		

B–8	0 1	0 1	0 1	0 1	0–1	0–1	2	3	3	3+	4	+							No further changes
B [illegible]	0–1	0–1	0–1	0–1	0–1	2	3	3	4	4	5	5	5	5+	5+	6	6		
B–30	0–1	0 1	0–1	0–1	0 1		3	3	3	4	4	4+	5	5	5	5	5		

2 r once monthly × 10

B–12?	0–1	0 1	0 1	0–1	0–1	0 1	2	2+	3	4	4	4	4	4	4+	4+	4+	5	
B–1?3	0–1	0–1	0–1	0–1	0–1	2	2	3	3	4	4	4	4+	5	5	5	5	5	
B 124	0–1	0 1	0–1	0–1	0–1	2	–	3	3	3	4	4	4	4	4	4	4	4	
B–1 5	0–1	0 1	0–1	0–1	0–1	1	2	2	+										No further changes
B–127	0–1	0–1	0–1	0–1	0–1	1	2	3	3+	4	4	4	5	5	5	5	5	5	
B 129	0 1	0–1	0–1	0–1	0–1	0–1	1	2	3	3	3	4	4	4	4	4	4	4	

50 r (once monthly × 10) total 500 r

Similar to the 25 r group first lens changes were seen biomicroscopically around 4 to 5 months after initial exposure The rate of progression of visible lens changes was almost equal to the 25 r group though individual lens changes were slightly more servere at any given examination date A final plateau with a grade 5+ was reached between the 18th month and 20th month after first irradiation (Fig 2 2) Range in severity at each individual given examination date within this group is presented in Table 2 2

100 r (once monthly × 10) total 1000 r

Onset of first observable lens changes was similar to the above two groups between the 4th and 5th months post initial radiation The rate of progression was slightly greater and the degree of lens changes was more severe at each given examination date A final plateau was reached between 18 and 20 months after first radiation exposure with a grade 6+ (Fig 2 2) Range is tabulated in Table 2 2 Total observation time was extended over 4 years for all groups

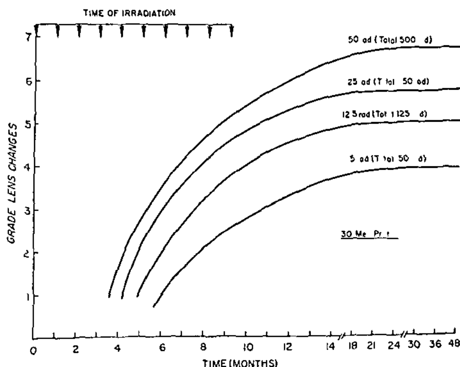


Fig 2 3

Onset and progression of lens changes exposed to a 30 Mev proton beam and four dose levels (5 12 5 25 50 rad) once monthly for 10 months

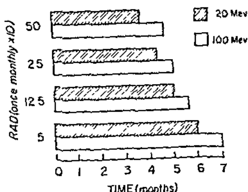


Fig 2 4

Comparison of l tent periods between initial irradiation and first appearance of *in vivo* observable lens changes for two proton beam energies (30 and 100 Mev) and four dose levels (5 12.5 25 50 rad)

Protons (100 Mev energy)

The experimental animals exposed to this energy were divided into four groups receiving 5 12 5 25 and 50 rad respectively once monthly over ten months The total doses thus administered were 50 125 250 and 500 rad

For the group which received only 5 rad monthly first minimal changes were seen about 6 months after initial irradiation i e at a time when a total *of 6 exposures had been given There was a slow gradual increase in lens chan*ges which about 2 years post first irradiation resulted in a plateau After this time no further changes occurred over a total observation time of 4 years (Fig 2-3 and 2-4)

For the dose groups (total 125 250 and 500 rad) the onset of observable lens changes appeared slightly earlier i e with higher doses the latent periods between first irradiation and visible lens changes were shorter For the highest dose (50 rad) approximately 3 5 months for the 25 rad group 4+ months and for the 12 5 rad group about 5 months (Fig 2 4)

The trend in progression of lens changes exposed to the various dose levels was quite similar though the severity in lens changes was quite significant and pronounced for each group

Final grades of lens changes were reached for all groups about 18 months post initial irradiation exposures (Fig 2 3) The range in severity of lens changes for all dose groups and any given examination time is presented in Table 2 3 The final grade of lens changes is presented *in Figs 2 3 and 2 6*

Table 2 3

See caption of Table 2 1 with the exception that the lenses had been exposed to a proton beam (30 Mev) at the SREL Synchrocyclotron

30 Mev proton beam

Examination (in months) post 1st exposure

Pabbit #	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20 – 48 months
50 rad once monthly × 10																					
S-1	0-1	0-1	0-1	0-1	0-1	2	2+	3+	4	5	5	5	6	6	6	6	6+	6+	+		
3	0-1	0-1	0-1	0-1	2	3	4	5	5	6	6	6	6+	7	7	7	7	7	7	7	
26	0-1	0-1	0-1	0-1	2	3	3	4	5	5	5	6	6	6	6+	6+	7	7	7	7	No further changes
27	0-1	0-1	0-1	0-1	0-1	2	3	4	5	5	6	6	6	6+	7	7	7	7	7	7	
28	0-1	0-1	0-1	+																	
29	0-1	0-1	0-1	0-1	2	2+	3+	4	4+	5	5	5	6	6	6	6	6	6	6	6	
25 rad once monthly × 10																					
6	0-1	0-1	0-1	0-1	0-1	2	3	4	4	5	5	5	6	6	6	6	6	6	6	6	
7	0-1	0-1	0-1	0-1	0-1	2	3	3	4	4	4	5	5	5	5	5	5	5	5	5	
8	0-1	0-1	0-1	0-1	0-1	0-1	2	3	4	4	4	5	5	5	5	5	5	5	5	5	
11	0-1	0-1	0-1	0-1	0-1	2	3	3	4	4	[illegible]	5	5	6	6	6	6	6	6	6	No further changes
31	0-1	0-1	0-1	0-1	0-1	2	3	3	4	4+	5	5	5	6	6	6	6	6	6	6	
32	0-1	0-1	0-1	0-1	0-1	2+	3+	4+	5	5	5+	6	6	6	6+	6+	6+	6+	6+	7	
33	0-1	0-1	0-1	0-1	0-1	2	[illegible]	4	4	[illegible]	[illegible]	5	[illegible]	5	[illegible]	[illegible]	[illegible]	+			

12.5 rad once monthly × 10

5	0-1	0-1	0-1	0-1	0-1	0-1	?	3	3+	4	4	5	5	5	5	5	5	5	5	+	
12	0-1	0-1	0-1	0-1	0-1	0-1	0-1	2	3	3	4	4	4	4	4+	4+	4+	5	5	5	
13	0-1	0-1	0-1	0-1	0-1	0-1	?	2	3	3	4	4	5	5	5+	5+	5+	5+	6	6	No further changes
14	0-1	0-1	0-1	0-1	0-1	2	2	3	4	4	5	5									
34	0-1	0-1	0-1	0-1	+																
3	0-1	0-1	0-1	0-1	0-1	0-1	?	3	3	4	4	4	5	5	5	5	5	5	5	5	
36	0-1	0-1	0-1	0-1	0-1	0-1	?+	3	4	4	4	4	5	5	5	5	5	5	5		

5 rad once monthly × 10

15	0-1	0-1	0-1	0-1	0-1	0-1	0-1	2	2	3	3	3	3+	4	+							
18	0-1	0-1	0-1	0-1	0-1	0-1	0-1	2	2	2	3	3	3	3	3	3	3	+				
30	0-1	+																				
39	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1	2	2	?	3	3	3	3	3	3	3	3	3	3	3+ No further changes
40	0-1	0-1	0-1	0-1	0-1	0-1	?	2	3	3	3	3+	4	4	4	4	4	4	4	4	4	4
41	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1	?	3	3	3	3	4	4	4	4	4	4	4	4	4
100	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1	2	2	2+	3	3	3	4	4	4	4	4	4	4	4

Table 2 4

See caption of Table 2 1 with the exception that the *proton beam energy was 100 Mev*

100 Mev proton beam																					
Examination (in months) post 1st exposure																					
Rabbit #	Pre	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20 – 48 months
50 rad once monthly × 10																					
S–19	0–1	0 1	0–1	0–1	0–1	0–1	2	3	3	4	4	+									
20	0 1	0–1	0–1	0–1	0–1	2	3	3	4	4	5	5	5	5+	+						
22	0–1	0–1	0–1	0–1	0–1	2	3	4	4	5	5	5	5+	6	6	6	6	6	6	6	No further changes
42	0 1	0 1	0–1	0–1	0–1	0–1	2	3	3+	4	4	4	5	5	5	+					
43	0–1	0 1	0–1	0 1	0–1	1	3	3+	4	4	5	5	5	5	5	5	5	5	5+	5+	
44	0 1	0 1	0–1	0–1	0–1	0–1	2	3	4	4	4	5	5	5	+						
25 rad once monthly × 10																					
S–25	0 1	0–1	0–1	+																	
45	0–1	0 1	0–1	0–1	0–1	0–1	2	3	4	4	4	5	5	5	5	5	5	+			
46	0–1	0 1	0–1	0–1	0–1	0–1	2	3	3	4	4	4	4	5	5	5	5	5	5	5	No further changes
47	0–1	0–1	0–1	0–1	0–1	0–1	1	2	3	3	4	4	4	4	4	4	4	5		5	
74	0–1	0–1	0–1	0–1	0–1	0–1	2	3	3	3	3	4	4	4	4	4	4	4	4	4	
75	0–1	0–1	0–1	0–1	0–1	0 1	2	3	3	4	4	4	5	5	5	5	5	5	5	5	

I ad onc m nthly × 10

S-₀0	0 1	0 1	0-1	0 1	0-1	0 1	2	-	3	3	3	4	4	4	4	4	4	4	4	4+
51	0-1	0-1	0 1	0 1	0-1	0 1	1	2	2	3	3	3	3	3+	4	4	4	4	4	4
53	0 1	0-1	0-1	0-1	+															
4	0-1	0-1	0-1	0-1	0-1	0-1	?	?+	3	3	4	4	4	4	4	4	4	4	4	4 No further changes
80	0-1	0-1	0-1	0-1	0-1	0-1	0-1	2	2	?+	3	3	3	3	3	3	3+	4	4	4
81	0 1	0-1	0-1	0-1	0-1	0-1	0-1	1	2	2	3	3	3	3	4	4	4	4	4	4
85	0-1	0-1	0-1	0-1	0-1	0-1	0-1	2	3	3	3	3+	4	4	4	4	4	4	4	4

rad once monthly × 10

55	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1	2	+										
6	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1	2	?	?	+							
60	0-1	0-1	0-1	0-1	0-1	0-1	0-1	2	2	3	3	3+	3+	3+	4	4	4	4	4	4
86	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1	2	?	?	?	2	?	2	2	2	2	2	2+
88	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1	?	?	2	3	3	3	3	3	3	3	3 No further changes
91	0 1	0-1	0-1	0-1	0-1	0-1	0-1	0-1	0-1	?	?	2	2	?	3	3	3	+		
92	0-1	0-1	0-1	0-1	0-1	+														

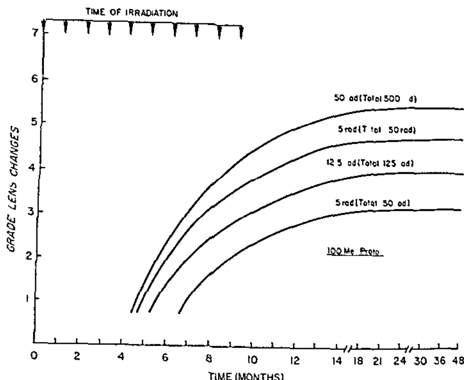


Fig 2 5

Onset and progression of lens changes exposed to a 100 Mev proton beam and four dose levels (5 12 5 25 50 rad) once monthly for 10 months

Protons (100 Mev energy)

Four dose levels were applied with exposures once monthly for a total of 10 months The doses were equal to those selected for the 30 Mev proton beam energy i e 5 12 5 25 and 50 rad First observable lens changes were noted between the 4th and 7th months post initial radiation with the shortest latent period for the highest dose level (Fig 2 4) Lens changes progressed in all lenses of the four dose groups and reached a final plateau after which no further changes were detectable by the methods employed in this investigation approximately 18 months after initial exposure to the 100 Mev proton beam (Fig 2 5) The final grades were 4 5 5 7 and 6 7 according to the grading system applied and described in Part I of this study and for the dose levels of 5 12 5 25 and 50 rad respectively (Figs 2 5 2 6) The range of lens changes within each group for given examination times is compiled in Table 2–x

Conclusions

X ray

While in the case of single X ray exposure to 25 r a final plateau was reached

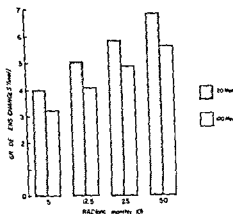


Fig 2 6

Comparison of final grades of lens changes for various dose levels and two proton beam energies

after about 8 months post irradiation progression of lens changes following fractionated radiation to 25 r over 13 weeks totalling 1000 r extended to about 1? months post initial radiation

Comparing the final grades of lens changes for the two groups (19 3 r and 25 r (?50 and 1000 r total) over 13 weeks) with lenses exposed to corresponding single doses (i e 250 and 1000 r) it is quite obvious that the severity for single exposures at these dose levels is more pronounced in the case of single exposure particularly for the higher dose level This can be expected and has long been recognized and attributed to a biological repair mechanism in the case of protracted exposures (Figs 1 2 2 1) Also the rate of progression of lens changes in the three groups exposed to 25 50 and 100 r once monthly over 10 months thus giving a total final dose of 250 500 and 1000 r respectively was–as one would anticipate–much slower if compared with progression of lens changes exposed to identical total doses given as a single exposure (i e 250 500 and 1000 r) Also the degree of final severeness of lens involvement was less pronounced as seen after single exposure for each given dose level

While protracted irradiation over 13 weeks giving a total of 250 and 1000 r respectively also resulted in significantly lesser lens changes as compared with those developing in lenses irradiated with the same dose in one single exposure it appears of interest that if exposures were given once per month totalling the same dose as given in the 13 weeks groups the final degree of lens changes was equal for these two groups Hence the time delay between individual exposures did not seem to influence the final degree of lens changes

Proton (30 Mev energy)

The final grade with a mean of grade 4 for the group having received only 5 rad per month (total 50 rad) was surprising, for it was only slightly and insignificantly lower than that for lens changes observed after a single exposure to the same total dose of 50 rad (Fig 1–3 and 2–3)

The observation, that with higher doses first detectable lens changes seem to occur earlier, is another factor which should be taken with caution for there is little justification biologically at least to support this subjective impresion (Fig 2 4)

When the final lens changes after single and fractional irradiation are compared, it becomes obvious that after single exposure a plateau was reached in all instances about 12 months post irradiation whereas in the case of protracted radiation (within the limits of these experiments) a plateau was not reached before the time limit of 18 months after first exposure (Figs 1 3 1 4 and 2 3 2 5) This observation can of course be anticipated if one considers the fractionated irradiation schedule

It furthermore seems remarkable that in case of very low dose levels time did not play a major role and final severity of lens chnges did not appear to be of significant difference after equal single or total fractionated radiation as mentioned above

To illustrate this observation it may serve as an example that for higher doses the final plateau i e reaching a degree after which no further significant lens changes occurred became quite pronounced In those cases where final end points are compared the degree of lens opacities which developed in the fractionated groups having received about 250 rad corresponded to lenses which had received a total single dose of about 100 rad For the 500 rad protracted dose group the changes were about equal to those observed in lenses exposed to a 250 rad single dose but equal energies of 30 Mev

Comparing the onset of lens changes after the first exposure to the two energies (30 and 100 Mev) applied in this investigation but equal dose levels (5 12 5 25 and 50 rad) one will note that the latent period was slightly longer for the 100 Mev energy beam exposure 6 vs 7 months for the 5 rad groups 5 vs 5 5 months for 12 5 rad 4+ vs 5 months for 25 rad and 3 5 vs 4 5 months for the 50 rad groups (Fig 2 4) This observation was not made for single exposures to the two beam energies (Figs 1 3 and 1 4)

Further progression of lens changes seemed to be similar in all groups exposed either to the 30 Mev or 100 Mev proton beams and is represented by the slope of the curves illustrating the grade of lens changes at given observation times (Figs 2 3 and 2 5) Also reaching a final plateau after which no further lens changes were noted for a total of 4 years observation time was equal for all groups exposed either to the 30 or 100 Mev energy beams i e 18 months after first exposure However the final degree of lens changes was more severe for

the lower LET (30 Mev) by approximately one grade of the grading system applied and described in detail in Part I of this report for the 5 rad groups (30 Mev vs 100 Mev) grade 4 vs 3+ 12 5 rad groups grade 5 vs 4 25 rad groups 5 / vs 4 / and for the 50 rad groups grade 6 7 vs 5 5 (Fig 2 6)

Protracted proton irradiation with a monthly dose of 5 12 5 25 and 50 rad and 100 Mev energy over a 10 month period thus revealed the following observations

Onset of first observable lens changes occurred between 4 5 and 7 months after first exposure This onset corresponded to the dose level The lowest dose caused delayed onset of minimal changes within the stated range The initial *slope of the curves corresponded to the ones seen in the graphs* illustrating the *development of lens changes after protracted exposures to* X *rays* A final plateau was *reached approximately 18 months post first exposure*

For a beam energy of 20 Mev the onset of first *detectable lens changes* occurred somewhat earlier than those *observed* with the *greater beam energy* of 100 Mev but equal total doses However there was also *some delay of onset in lens* changes of those exposed to lower doses The *range was from* about *3 5 to 6* months post initial irradiation The slopes of the curves closely approximated those plotted for the 100 Mev group although there is a significantly greater effect on all lenses for each dose of the lower when compared with a similar dose but higher beam energy No further increase in lens opacities occurred after the 18th month post initial irradiation

In general the slope of the single dose proton beam irradiation indicating the progression of lens changes was less steep than observed for previous single X ray dose exposures For the single proton exposure a plateau was reached *about* one year after exposure while for single X ray exposure a plateau was *usually already* observed 6 months post irradiation after which no significant changes in lens opacities occurred

Progression of *lens changes* and final plateau formation within each group were significant and *depended on the* dose applied This was characteristic for the mode of irradiation (i e *single dose or protracted* dose) as well as for the type of irradiation (i e X ray or *proton beam*)

For single and protracted exposures to a *proton* beam the lens changes were certainly influenced by the beam energies *The changes* were *significantly* greater with lower beam energy (Mev) though equal doses in rads

The final degree of lens changes were about equal if the *total fractionated* dose given (once per month over 10 months) was about twice that of a single exposure i e 500 r (X ray) given over 10 months had the same effect as 250 r (X ray) given as a single dose This observation also holds true for single and fractionated proton beam irradiation (within the limits of this investigation)

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Further progression of lens changes seemed to be similar in all groups exposed either to the 30 Mev or 100 Mev proton beams and is represented by the slope of the curves illustrating the grade of lens changes at given observation times (Figs 2 3 and 2 5) Also reaching a final plateau after which no further lens changes were noted for a total of 4 years observation time was equal for all groups exposed either to the 30 or 100 Mev energy beams i e 18 months after first exposure However the final degree of lens changes was more severe for

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Further progression of lens changes seemed to be similar in all groups exposed either to the 30 Mev or 100 Mev proton beams and is represented by the slope of the curves illustrating the grade of lens changes at given observation times (Figs 2 3 and 2 5) Also reaching a final plateau after which no further lens changes were noted for a total of 4 years observation time was equal for all groups exposed either to the 30 or 100 Mev energy beams i e 18 months after first exposure However the final degree of lens changes was more severe for

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Further progression of lens changes seemed to be similar in all groups exposed either to the 30 Mev or 100 Mev proton beams and is represented by the slope of the curves illustrating the grade of lens changes at given observation times (Figs 2 3 and 2 5) Also reaching a final plateau after which no further lens changes were noted for a total of 4 years observation time was equal for all groups exposed either to the 30 or 100 Mev energy beams i e 18 months after first exposure However the final degree of lens changes was more severe for

Results and Discussion*

A. Single dose (x ray) Irradiation

125 r onset slope and final degree are almost identical to 100 r single X ray dose of older AEC studies and therefore fall well in place with those previously plotted data ranging from 25 r to 1000 r single dose (Fig 1 2)

B Protracted doses (x ray)

25 50 and 100 r once monthly over a total of 10 months giving a total dose of 250 500 and 1000 r respectively (Fig 2 2)

1 First lens changes were seen in all three groups around the 4th month following first lens exposures

2 The initial slope of all curves at the time interval 4 to 8 months post first exposures was somewhat similar to that of the 125 r single exposure (see above)

3 All three curves (250 500 and 1000 r) came to a plateau around the 13th 14th month after first or about 4 months after the final exposure

4 The final plateau for the three different exposures corresponded approximately

250 r protracted dose = 125 single dose
500 r protracted dose = 200++ single dose
1000 r protracted dose = 600 single dose

C Single dose (Proton beam) Irradiation (Harvard University Synchrocyclotron)

1 25 50 100 250 rad/20 Mev (Fig 1 3)

Onset of lens changes for all four doses about 4 months after exposures

a Between onset of lens changes up to 7 to 8 months post irradiation the curves are almost identical to the ones described for each similar dose but with a beam energy of 100 Mev

b The final plateau for each dose was slightly but significantly higher than the one for lenses exposed to higher beam energy (100 Mev)

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*Classification and grading of lens changes were discussed in detail in Part I of this report Reference to figures and tables are given in two numbers the first indicates the part in which the original figure or table was presented, the second number represents the figure in that part

PART III

COMPARISON OF DATA DESCRIBED IN PART I AND PART II

Brief summary of the radiation schedule for single and fractionated doses

A Single dose (x ray)

125 r supplement previous studies on single dose X ray exposures ranging from 25 to 1000 r under AEC contract (Ref 1 and 2)

B Fractionated x ray irradiation

19 3 r 1 × weekly for 13 weeks with a total of 250 r
25 r 3 × weekly for 13 weeks with a total of 1000 r
25 r 1 × monthly for 10 months with a total of 250 r
50 r 1 × monthly for 10 months with a total of 500 r
100 r 1 × monthly for 10 months with a total of 1000 r

C Single dose proton beam

(Harvard University Synchocyclotron)		(SREL)
1) 25 rad/20 Mev	2) 25 rad/100 Mev	3) 25 rad/100 Mev
50 rad/20 Mev	50 rad/100 Mev	125 rad/100 Mev
100 rad/20 Mev	100 rad/100 Mev	500 rad/100 Mev
250 rad/20 Mev	250 rad/100 Mev	

D Fractionated proton beam (SREL)

1) 5 rad/100 Mev	2) 5 rad/30 Mev	1 × monthly for 10 months with a total dose of 50 125 250 and 500 rad
12 5 rad/100 Mev	12 5 rad/30 Mev	
25 rad/100 Mev	25 rad/30 Mev	
50 rad/100 Mev	50 rad/30 Mev	

d The degree of lens changes corresponded to an equal protracted dose of X ray irradiation (Figs 2-2 and 2-5)

9 5 12 5 25 50 rad/30 Mev given over 10 months once monthly giving a total dose of 50 125 250 and 500 rads total dose (Fig 2 3)

a The on t of first detectable lens changes occurred somewhat earlier than those observed with the greater beam density of 100 Mev but equal doses However there was also some delay for onset of lens changes of those exposed to lower doses The range was from about 3 5 to 6 months post initial irradiation

b The configurations of the curves closely approximate those of the 100 Mev group although there is a significantly greater effect in all lenses for each dose as compared with a similar dose but higher beam energy

c No further increase in lens opacities occurred after the 14th 18th month post initial irradiation

Conclusions

(beyond those listed in Part I and II)

1 In general the slope of the *single dose proton beam irradiation indicating* the progression of lens changes was *less steep than that observed for previous* single X ray dose exposures For the single proton beam a plateau was reached about one year after exposure while for single X ray *exposure a plateau was* usually observed already 6 months post irradiation i e after this time no significant changes in lens opacities occurred

2 Progression of lens *changes and final* plateau formation within each group were significant and depended *on the dose applied* This was true for the mode of irradiation (i e single dose or protracted dose) as well as for the type of irradiation (i e X ray or proton beam)

3 In general it can be stated that for acute and fractionated exposures to equal total dose levels *deviations* in severity of observed lens *changes* are significantly more pronounced *after exposure to* high dose levels and may be quite insignificant for lower doses *The reason for* this observation may lie in the fact that more subtle and minute changes are more difficult to classify by subjective viewing as inherent in these studies

4 For single and protracted exposures to a proton beam the lens changes were slightly but significantly *greater* with lower beam energy (Mev) though equal doses in rad

2 25 50 100, 250 rad/100 Mev (Fig 1 4)

Onset of first lens changes for all four doses around the 4th month after exposure

a The curve for 25 rad/100 Mev corresponds in slope and final degree of lens changes to a single X ray exposure of 125 to 50 r but more closely to the 25 X ray plot

b The curve for 50 rad/100 Mev is almost identical to the 50 r X ray plot

c The initial slope for the curve representing 100 rad/100 Mev corresponds to the 100 r single X ray dose up to about 8 months post irradiation The final plateau corresponds more to the plot representing 200 r single X ray dose and was reached at approximately 12 to 13 months after exposure

d For 250 rad/100 Mev the curve was also more flat" and the final plateau reached at about 12 months post irradiation corresponded to 500 r single X ray exposure

3 25 500 rad/100 Mev (SREL) (Fig 1–5)

Onset of first lens changes for the three doses between the 4th and 5th months after exposure

a The lens changes for 25 rad/100 Mev were similar to those produced at the Harvard University Synchrocyclotron

b Observed lens changes for 125 rad/100 Mev corresponded to those of 100 rad/100 Mev exposures at Harvard University

c Exposures to 500 rad/100 Mev produced lens changes almost identical in development and final degree to those exposed to 250 rad/100 Mev at the Harvard Synchrocyclotron This unexpected observation can at present only be explained by variations in dosimetry and/or by the age of the rabbits at the time of exposure (4 to 6 weeks old at the time of irradiation at the Harvard Synchrocyclotron vs 8 to 12 week old rabbits exposed at SREL)

D Protracted dose (Proton beam) irradiation (SREL)

1 5 12 5 25 50 rad/100 Mev given over 10 months once monthly thus giving a total of 50 125 250 500 rads total dose (Fig 2–5)

a Onset of first observable lens changes occurred between 4 5 and 7 months after first exposure This onset corresponded to the administered dose The lowest dose caused the most prolonged latent period before first minimal lens changes were visible

b The initial slope of the curves corresponds to the one seen in the graphs illustrating the development of lens changes after protracted exposures to X rays

c A final plateau was reached between 14 and 18 months post exposure

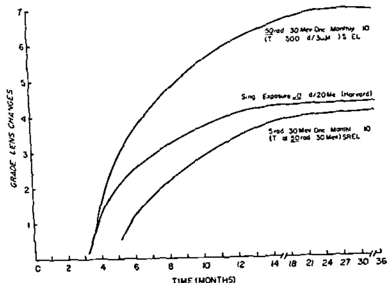


Fig 3 2
Caption same as in Fig 3–1 but notice different beam energy (100 Mev vs 20–30 Mev)

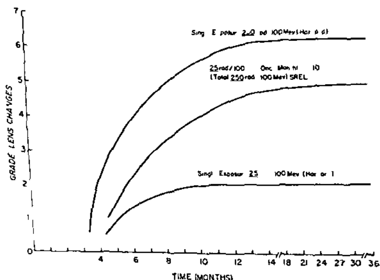


Fig 3 3
Th graph epresents three situations to compare Each of the curves represents either an equal n tial or final dose rate and its corresponding response Proton beam energy was equal (100 Mev)

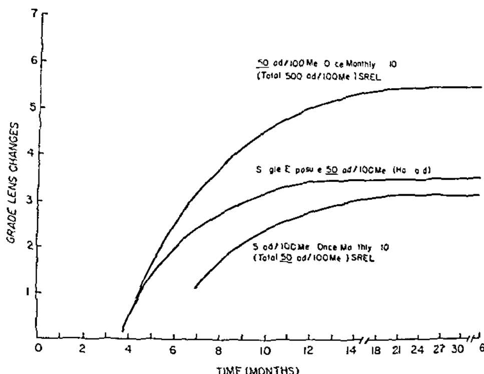


Fig 3 1

Comparison of lens changes after exposures to various modes of irradiation This graph represents three selected situations worth comparing The top curve shows lens change progression after fractionated exposure to a 50 rad/100 Mev proton beam (monthly × 10) The middle curve represents changes observed if 50 rad/100 Mev were given only as a single dose The lower curve demonstrates changes which occurred if only 5 rad/100 Mev were applied monthly over a 10 month period totalling 50 rad/100 Mev Note The proton beam energy was the same (100 Mev) Application periods were either single exposure or fractionated over 10 months

5 Of particular interest is the comparison of the curves showing some similarities

a

aa) 50 rad/100 Mev single dose proton irradiation

bb) 50 rad/100 Mev (total dose) received as fractionated proton irradiation over a period of 10 months

cc) 50 rad/100 Mev (individual dose given monthly for 10 months) – i e total of 500 rad/100 Mev (Fig 3–1)

b

aa) 50 rad/20 Mev single dose proton irradiation

bb) 50 rad/30 Mev (total dose received as fractionated proton irradiation over a period of 10 months)

cc) 50 rad/30 Mev (individual dose given monthly for 10 months – i e total of 500 rad/20 Mev (Fig 3–2)

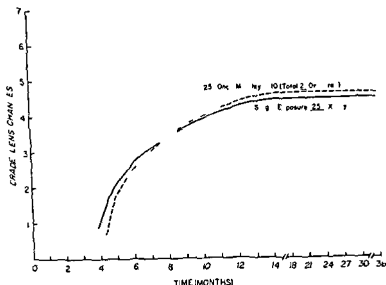


Fig 3 6
Comparison of effects of X ray irradiation on the lens with a 1 2 ratio (i e single vs protracted exposures) Note similarity in progression and final plateau of lens changes

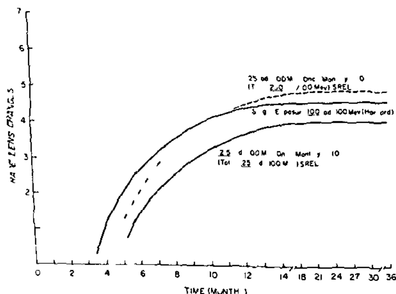


Fig 3 7
Comp a n of lens changes after *three radiation* schedules all with a proton beam energy of 100 Mev

54

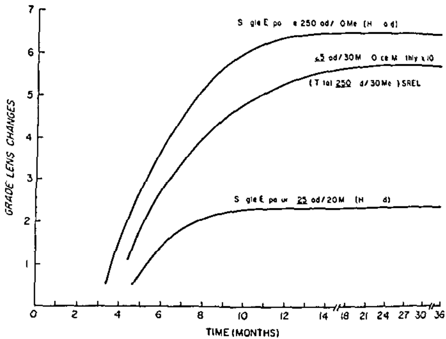


Fig 3-4

Same as capiton in Fig 3-3 with the exception that beam energy was °0-30 Mev instead of 100 Mev

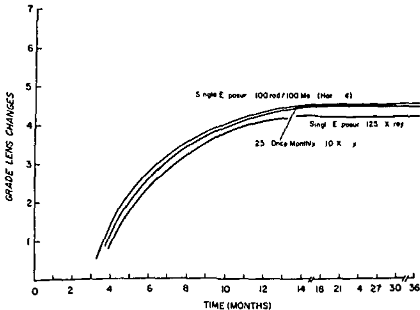


Fig 3-5

Comparison of lens changes observed after different types of irradiation Note similarity of lens progression and final lens changes for the various exposure schedules

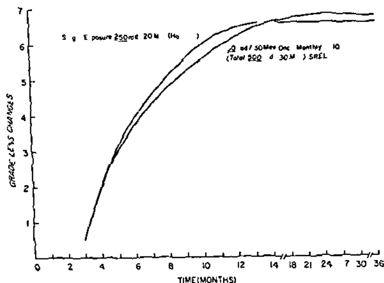


Fig 3 8

Comparison of a single exposure to a 20 Mev proton beam and a dose of 250 rad to a 50 Mev proton beam but fractionated doses of 50 rad once monthly for 10 months thus delivering a total dose of 500 rad. Note similarity in progression and final degree of lens changes for the two total dose levels

Table 3 1

+ (-) Lenses show slightly more or (less) opacity in comparison with other data in the same line

Single X r	Protract X - r	Single Proton rad		Protract Proton rad	
		20 Mev	100 Mev	30 Mev	100 Mev
5		25+	25		
50		50+	50	5+	12.5+/-
125	250	50++	100-	12.5	25
200	500+	100+	100+	25+	50
600	1000	200+	250	50+	

This comparison gives information about accumulation effects of as low as 5 rad monthly and the degree of such accumulation of doses as high as 50 rad given at a monthly rate for two beam energies i e 100 and 20 30 Mev

A similar comparison can be made on

c

aa) 25 rad/100 Mev single dose (Harvard University)

bb) *250 rad/100 Mev single dose (Harvard University)*

cc) 25 rad/100 Mev (individual dose per month for a total of 10 months) total *dose of 250 rad/100 Mev (Fig 3–3)*

d

aa) 25 rad/20 Mev single dose (Harvard University)

bb) 250 rad/20 Mev single dose (Harvard University)

cc) 25 rad/30 Mev (individual dose per month for a total of 10 months) total dose 250 rad/30 Mev (Fig 3–4)

From the comparison listed under Conclusions 4" one recognizes that the onset of the curve plotted from data 4 a (aa) and that of 4 a (cc) are equal (3 4 months post irradiation) This should be expected if the normal latent period of clinical lens changes of a few" months is accepted

At about 6 months however the two curves deviate with more progressive lens changes in the fractionated irradiated lens to a monthly dose equal to the initial single dose At 12 months after initial irradiation these differences in severity of lens changes are highly significant While the single irradiated lenses have reached a plateau" of lens opacity changes at that time the lenses irradiated with a fractionated dose came to a plateau about 14 to 18 months after first irradiation

Of particular interest is the comparison of curves 4 a (aa) with 4 a(bb) (Fig 3–1) The onset of the latter curve (5 rad per month) shows a pronounced delay (4 5 vs 7 months) after initial irradiation However from the time of onset in the single irradiated lens and the fractionated exposure (though to a 10 × lower dose) the slope of the 2 curves appear at present almost parallel This means that the latter is lacking in severity of lens opacities approximately one clinical degree of lens changes (as used in this study) behind the former

The final lens opacities of this group (50 rad/20 Mev total) approached the degree of singly exposed lenses (50 rad/20 Mev) This would mean a simple accumulation of lens changes under the given experimental conditions

Comparing the curves mentioned under 4 b (aa) 4 b (bb) and 4 b (cc) (Fig 3 2) one can make the same statement as that in the previous chapter (i e for a beam energy of 100 Mev) The degree of lens changes however is for all three curves somewhat more pronounced

Of similar interest is a comparison of curves from observations as produced by experiments covered under 4 c (aa bb cc) (Fig 3 3) Here for a given beam energy of 100 Mev 250 and 25 rads single proton irradiation are compared

b In support of point 1 above it should be stated that all gradings of lens pathology were conducted as a blind study i e the individual examiner was not aware of the type dose irradiated eye nor time at which the many groups of experimental animals to be examined had been irradiated Therefore bias due to memorizing of individual animals was impossible Also records of previous observations in each animal were not available to the examiner until the *study was terminated*

Acknowledgment

The authors are grateful for the extensive technical assistance rendered by Messrs Vernon Jones and Ronald Hale

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Other pertinent literature is listed in the above mentioned papers

with 25 rad/100 Mev as a fractionated dose given monthly for 10 months As one can expect the first lens changes occurred somewhat delayed with regard to 250 rad single initial dose and almost equal in time to 25 rad single time exposure However the 25 rad single irradiation effect came to a plateau very significantly lower than in the case of 25 rad monthly exposures The single dose of 250 rad on the other hand showed more effect on lens changes While these latter changes have come to a "standstill with regard to progression approximately 10 to 12 months after exposure the lenses exposed to 25 rad monthly over 10 months showed a progression in clinical observable lens changes up to 14 18 months after first exposure

Again similar observations at a slightly more pronounced degree for all given situations are made for similar doses in rads but for a lower beam energy i e 20 30 Mev instead of 100 Mev (Fig 3 4)

The various comparisons are illustrated in Figs 3 5 to 3 7 Of interest is the almost identical configuration of curves plotted from lens changes after single proton beam irradiation of 100 rad/100 Mev 25 r X ray exposures (X 1 monthly/10 months) and 125 r X ray (single) exposure (see Fig 3 5)

6 Table 3 1 compares approximate degrees of severity of lens changes for the various radiation groups The data are based on final severity of lens changes Differences in the slope of the curves have been described above, (A B C_1 + 3 E and Conclusions (1)) and are illustrated in graphs of Part I III of this report

7 The range of lens changes within each group is given at 6 month intervals on each graph representing the mean for each group in a solid line curve

8 The final degree of lens changes is about equal if the total fractionated dose given (once per month over 10 months) is about twice that of a single exposure i e 500 r (X ray) given over 10 months has the same effect as 250 r (X ray) given as a single dose (Example Fig 3 5)

This observation also holds true for single and fractionated proton beam irradiation (within the limits of this investigation) (Example Figs 3 6 and 3 7)

9 Other variations or relations may become more evident or prominent with further follow up studies being done at present

10 The following points are stressed since their significance is inherent in the reported findings

a Statements with regard to similarity of lens pathology – either in progressive or total lenticular changes – are regarded as being subject to fluctuations though within limits since all degrees of lens pathology were based on clinical subjective classifications Though it may be accepted that such determinations are frequently more exact than other more objective means of recording this point should be kept well in mind

has been shown to be a function of the exposure time With the very short exposure times afforded by the Q switched laser (nanosecond range) the relationship of energy density to the spot diameter is however theoretically negligible

The pigment epithelium is the site of the onset of damage due to the absorption of the photic energy (Fine & Geeraets 1965) This effect has been observed to occur predominantly in the smooth surfaced endoplasmic reticulum of the apical and midzonal cytoplasm It was shown to vary directly with the number of pigment granules per cell and is a function of the wave length of the impinging light (maximum effect $\lambda = 500$ 550 nm (Rounds 1965 Rounds et al 1965) At increased energy levels changes were also observed in the photoreceptor cells caused by heat conducted from the adjacent pigment epithelium Leure DuPree (1968) showed that the pigment epithelium provides metabolic support to the neural retina by transport of nutritive materials which must be considered a factor in the damage to the photoreceptor cells

A threshold lesion has been defined by various criteria The minimal ophthalmoscopically visible lesion criteria used by most investigators has been shown by Davis & Mautner (1969) to be only slightly dependent on the time of observation after exposure The threshold power density for immediate 10 minute and 24 hour post exposure observable lesions varied at the ratio of approximately 1 0 9 0 8 Histological evidence of damage has been found by Geeraets et al (1963) at levels of 10 to 20 per cent below the 5 minute post exposure ophthalmoscopic observation level Some changes in ERG patterns have been noticed at levels as much as 50 per cent below the ophthalmoscopic threshold by McNeer et al (1963) and Jones et al (1968) but these investigators were forced to irradiate exceptionally large areas of the retina in order to demonstrate the effect on the electroretinogram Geeraets et al (1965) and Fine & Geeraets (1965) discussed the effect of hot spots" in the pulsed ruby laser in determining the threshold and found that the energy required to produce a threshold lesion of a size identical to the irradiated area was one to two times that needed to produce a circumscribed hot spot lesion

The histopathology of the minimal pulsed ruby laser lesion has been well described (Geeraetes et al 1965 Zweng et al 1964 Jones & McCartney 1966 Marshall & Mellerio 1967) Changes have been shown to consist primarily of vacuolization in the pigment epithelial cells with mild adherence to the receptor cell layer the latter demonstrating subsequent increased affinity for various stains

Within the visible spectrum the threshold lesion has been found to be relatively independent of wave length as would be expected on the basis of the spectral data of Geeraets & Berry (1968) At exposure times where the data overlap those taken with coagulator units using a pulsed high pressure Xenon arc or a pulsed ruby laser device threshold agreement is remarkable (0 72 0 85 joules cm) (Geeraets et al 1965)

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From the Departments of Ophthalmology and Biophysics
Medical College of Virginia
Health Sciences Center Virginia Commonwealth University
Richmond Virginia

THE EFFECT OF PULSED RUBY LASER ON RETINAL PIGMENT EPITHELIUM IN VITRO

WALTER J GEERAETS VAN B NOAH and ALEXANDER M CLARKE

Since the introduction of the laser in 1960 many attempts have been made to ascertain threshold values for damage to the sensitive retinas of various mammalian eyes employing *in vivo* methods *In vitro* studies have been made by Rounds (1965) and Rounds et al (1965) on cells and tissues in culture and by King & Geeraets (1968) on the effects of Q switched ruby laser radiation upon explants of ten day old chick embryo retinal pigment epithelium The investigation presented here has been patterned after the latter study substituting a pulsed ruby laser thereby affording a pulse duration in the microsecond instead of the nanosecond range

Previous investigations (Geeraets et al 1965 Ham et al 1958 1965 1966) have demonstrated the dependence of retinal threshold damage by thermal energy density (irradiance) upon both duration of the exposure and the spot size of the retinal image The power density required to produce a threshold lesion has been shown to be inversely proportional to the diameter of the spot size for relatively long exposure times (> 100 ms) as a result of the greater heat dissipation associated with the smaller lesion geometry The threshold energy density

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which sampled a small portion of light energy via fiber optics to a detector and strip chart recorder Laser output was adjusted using glass cells containing $CuSO_4$ solution as attenuation filters Beam geometry was modified by various sized apertures (Fig 1) The transmission of the microscope and the calibration factor of the beam splitter were obtained using a double cone radiometer The set up was such that a laser pulse could be directed into the microscope system and onto the pigment epithelium in the Rose chamber and be simultaneously monitored on the strip recorder A Leitz achromat 25 × objective was used in the microscope whenever exposures were made

Time lapse cinephotomicrography using a Sage Instrument (Model 500) and a Bolex camera was performed during observation periods usually at a rate of four frames per minute A period of 20 minutes prior exposure to the laser was filmed as a control and observations were made after exposure for 45 to 90 minutes If cinephotomicrography was performed immediately after explantation of the pigment epithelium into the Rose chamber no movement of the pigment granules could be observed presumably an effect of manipulation When observed 24 hours later motion of the pigment granules was present particularly in the peripheral field of the explant where the cells were usually more active

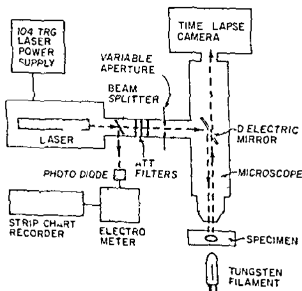


Fig 1
Schematic drawing of the experimental set up

Table I summarizes previous investigations for determining the threshold values of the pulsed ruby laser on retinal pigment epithelium *in vivo*

Table I
Pulsed Ruby Laser Threshold Burns on the *In Vivo* Rabbit Fundus

Authors	Retinal image diameter (μ)	Exposure time (μ sec)	Retinal energy density (J/cm²)	Retinal irradiance (KW/cm²)
Zaret et al (1963)	150	500	2.7–2[illegible].0	0.54–5.4
Geeraets et al (1965)	800	200	0.72	3.6
Fine & Geeraets (1965)	800	200	1.00	5.00
Ham et al (1966)	800	200–800	1.00	2.0–8.0
Jones & McCartney (1966)*	1125	150	8.00	2.0–[illegible]4
Kohtiao et al (1966)	250	500	0.16	0.3[illegible]
Campbell et al (1966)		700	0.65	0.93

* monkeys

Method and Materials

Pigment epithelium was obtained by microscopic dissection from ten day old White Leghorn chick embryos (selected because of the absence of choroidal pigmentation) A flat preparation of the posterior pole excluding the neural retina but including the choroid and sclera was made by inserting the explant into a modified Rose chamber with the pigment epithelial layer against the coverslip (King & Geeraets 1968) The anterior or equatorial region of the pigment epithelium was not used because of scattering throughout the larger binucleated cells (Coulombre et al 1963) The culture medium used was Minimum Essential Medium with 10 per cent calf serum containing buffered penicillin G 100 units/ml streptomycin sulfate 30 mg/ml and L glutamine 80 mg/ml Between experiments these Rose chambers were incubated at 40°C with a P_{CO_2} of 5 per cent

During the experimentation the Rose chamber explant side up was placed on the 40°C heated stage of a T R C model 104 Biolaser consisting of a binocular phase contrast microscope (Leitz) connected to a pulsed ruby laser (wave length of 694 3 nm and pulse duration of 800 μ sec) The optical arrangement between the laser exit window and the microscope contained a beam splitter

mined from the amount of energy causing minimal damage to the entire area of the spot size of 125 μ diameter with no damage outside of this area For this spot size the energy density was 2 36 j/cm² and the retinal irradiance was 2 95 KW/cm determined by dividing the total energy or power of the beam by the area of 1°5 μ diameter as in the study by King & Geeraets The threshold for minimal damage to the migrating pigment epithelium appeared to be identical with that of the initial explant

The threshold irradiation was characterized by a mild dissociation of the cells a few minutes post exposure (Fig 3) over the entire 125 μ diameter At exposure levels as low as 1 3 j/cm² some damage was observed over a smaller area than that being irradiated but with energy densities lower than this there was no effect When the migrating pigment epithelium was exposed there was also cessation of granular motion at values as low as 1 3 j/cm² At times some ad herence of the cells occurred around the exposure level of 2 36 j/cm² As the exposure was increased to two times threshold gross coagulation of the cells in the center and retraction of the peripheral cells to form a much larger lesion occurred as well as disruption of cellular morphology and dispersion of pig ment At two to three times threshold a clearing of cells centrally was noted and with exposures of slightly over three times threshold a bubble was formed in the center of the exposed field which rapidly disappeared

With the 369 μ aperture a beam of approximately 5 μ diameter was incident on the pigment epithelium layer It is assumed that the use of this aperture should not change the energy density on the explant Irradiations at approxi mately 1 36 j/cm² 1 40 j/cm² and 2 42 j/cm² all produced a five micron dia meter spot or pigment dispersion within the cell exposed In this latter part of the experiment only migrating pigment epithelium was used

Discussion and Conclusions

It is imperative to repeat that the term threshold always has to be defined within the terms in which it is used in the experiment because threshold values for different end points or examination techniques can vary considerably

The difficulty in properly characterizing a beam of this nature in one experi ment when comparing it with another is obvious Since in this investigation the same experimental apparatus was used as in the previous experiment with the ruby laser in Q switched mode (King & Geeraets 1968) the beam diameter has been assumed identical The damage mechanisms however although similar are not identical The abbreviated laser pulse in Q switched operation occurs over such a short time span that normal thermal relaxation phenomena cannot occur This results in an explosion like event in the melanin granules at exposure levels

In this region the cells migrated toward the periphery and showed general two dimensional enlargement

Using the method of King & Geeraets most of this study was done with a 125 μ image diameter (no aperture inserted) A 369 μ diameter aperture was also used yielding an image of 56 μ diameter at the pigment epithelial plane.

Results

Following its placement into the Rose chamber the explant of retinal pigment epithelium immediately displayed very little if any cellular motion Marginal cells demonstrated granular motion and tended to migrate peripherally which precipitated the loss of some degree of the uniformity in the characteristic hexagonal shape These cells exhibited an approximate 75 per cent enlargement after 24 hours in the two dimensional plane over the initial cells of 8 10 μ diameter probably due to flattening These migrating cells did therefore not appear quite as densely pigmented as the cells of the initial explant as would have been expected

The dependence of the lesion size on the energy density incident on the retinal pigment epithelial cells is explained by the Gaussian distribution of the energy across the beam diameter (Fig 2) The threshold for cellular death was deter

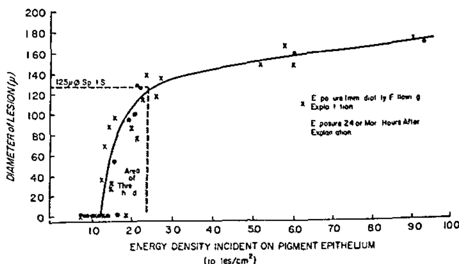


Fig 2

Relationship between energy incident on retinal pigment epithelial cells *in vitro* for a beam diameter of 125 μ at this cellular plane and the diameter of the resulting lesion.

only slightly above threshold and a very sharp demarcation between the damaged and undamaged cells. This is in contrast to observations made after exposure to the considerably longer pulse durations of 800 μ seconds as used in the present study. Specifically, no thermal averaging takes place for the Q switched case, which accounts for the localized cell damage occurring at 5 to 10 per cent of the 800 μ second exposure energy density found in this study.

In considering the value that should be taken as the "threshold" criteria for this experiment, the minimum observable irreversible effect occurred at 1.36 j/cm² for both the 125 μ and the 5 μ beam diameter at the pigment epithelial plane. This is in excellent agreement with the value found for the same criteria *in vivo* (Ham et al. 1966).

Only a small "size effect" should be expected for the exposure time beam geometry used, based on the transient case thermal models of Vos (1963) and Mainster et al. (1970). This effect, if present, was masked by the dissimilarities between the "averaging" of the pigmentation for the large diameter beam and the specific pigment distribution of the irradiated sites in the cell for the smaller beam and is not affected by the relatively pure optical quality of the experimental eye (Ham et al. 1969).

The advantages of this *in vitro* experiment were obvious: closely controlled beam geometry and energy measurement not affected by the changes in ocular parameters of the experimental animal, observation under high magnification with precision optics, thus obviating the problem of contrast recognition at small image diameters *in vivo*, and an easily reproduced criterion of damage. It must be noted, however, that the very small image size used in this *in vitro* study is a "worst case" approximation of a possible accidental exposure to a laser beam in man. In such accidental exposures the image size of the laser beam on the retina may approach this minimum size limit, but is dependent on the imaging ability of the coagulation unit and the lesser optical qualities of the eye.

Summary

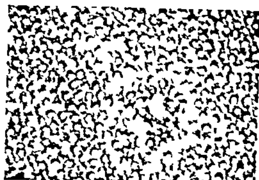
An *in vitro* method of determining the threshold value of damage by a pulsed ruby laser to the retinal pigment epithelium of chick embryo has been described. This value was found to be 1.36 j/cm², approximating the value found by *in vivo* methods. Reduction of retinal image size did not increase the *energy density* requirements for threshold injury as it has done with the *in vivo* methods. Confirmation of the relationship of threshold energy requirement with the duration of the pulse is made.



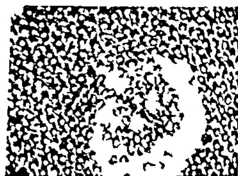
CONTROL



15 MINUTES



EXPOSURE



30 MINUTES



5 MINUTES



45 MINUTES

Fig 3

Chick embryo retinal pigment epithelial explant exposed to 3 42 J cm (3 0 KW cm) of a pulsed ruby laser (800 μ sec exposure time) The given times indicate progression of changes observed after exposure by time lapse cinephotomicrography Negative prints are used to enhance contrast (× 150)

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Paufique & Shapland (1951) modified this intervention so as to make it less hazardous They performed a lamellar resection, leaving intact the deepest portion of the scleral layer which was cauterized by diathermy After suturation of the scleral margins the result was an inward bulge of the remaining scleral layer and the choroid The resection was located at the site of retinal rupture the intervention consequently approaching the technique that now has become dominant

Custodis s (1951) plombage method convincingly demonstrated the effective ness of scleral impression Plombs made of some elastic material were affixed outside the sclera over the site of the rupture after diathermy of the sclera The plomb was attached by means of mattress sutures which when tightened deeply depressed the sclera at the right spot Custodis s idea was to close the rupture with a valve The intervention led to the important observation that if the bulge was placed exactly over the rupture the elevation would often disappear within 24 hours whereas the elevation remained wholly unaffected if the bulge was located beside the rupture

A further step in the development of buckling operations was the advent of the encircling technique introduced by Schepens (1957) An equatorial lamellar strip was resected and after cautery by diathermy a polythene tube with a nylon thread passed through it was placed in the groove When the thread was pulled tight a circular impression was created Schepens felt that this would produce a barrier behind the rupture(s) separating the ruptured area from the normal retina i e usually from the entire posterior portion of the fundus According to Schepens the action of the bulge itself was associated with reduced traction in vitreous filaments attached to the retina Arruga s suture (1957) is a well known variant of this technique It takes the form of a circum equatorial suture which is pulled tight The impression thus produced differs from that caused by Schepens s polythene tube by being deeper Arruga explained the effect of this intervention by volume reduction

Although the effectiveness of these methods has been amply documented by long experience there is some discord as to why they are effective and partic ularly how to explain their ability to make the elevation disappear Theories on this can be sorted into three categories

With respect to the theory of volume reduction to account for the effective ness of buckling operations it is conceivable that this would bring the choroid into closer contact with the retina It should be kept in mind however that the retina might snap back rapidly and the permanence of such contact must be considered unreliable To establish reliable contact some form of pressure must act also from the vitreous side but these theories make no allowance for this

Custodis believed that the scleral bulge acted as a valve and closed the rup

From the University Eye Clinic Goteborg Sweden

SIGNIFICANCE OF SUBRETINAL ABSORPTION FOR EFFECTIVENESS OF BUCKLING OPERATIONS

BY

BENGT ROSENGREN

The main advantage of buckling interventions in the surgical treatment of retinal detachment is that they may abolish an elevation and thus enable the retina and choroid to reattach themselves to one another How this comes about remains unclear however

The historical development of these interventions follows no consistent course They have instead been proposed on the basis of various theoretical considerations some of which subsequently have proved more or less inadequate They have mainly been evolved from empirical observations which piled on top of one another have combined to produce technical interventions of high effectiveness

The first deliberate attempt to force the retina against the choroid was presumably *Lindner s introduction (1933) to modern detachment surgery* of Leopold Muller s scleral resection Lindner modified this and as a rule resected only along half the equatorial circumference as the first step The resected scleral strip was between 2 and 6 mm wide and when *the scleral margins were sutured* together the scleral capsule became reduced in size No information is given on how the resections were located in relation to any ruptures cautery was not consistently used Lindner s aim was to reduce the volume of the scleral capsule so that it would fit the detached retina better Volume reduction became a theoretical slogan which long pursued operations on the retina

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pressure elevation In this case things took a different course As much as 0 45 ml could be injected on each occasion probably owing to the pronounced hypotension Significantly when 3 ml had been injected into the vitreous the pressure returned to normal and remained so at the last follow up examination 2 months after the course of injections

In my view this normalization of the pressure requires an explanation Since neither the inflow mechanism nor the outflow through the trabecular network could have been affected by any of the interventions the reason must be looked for elsewhere The inert substance injected little by little filled the vitreous and when this had been almost replaced by silicone fluid the intra ocular pressure became normal This suggests that prior to the silicone injections passage had taken place from the vitreous space to the subretinal space and that such passage was blocked when most of the vitreous substance had been replaced by silicone fluid This implies that the ultimate cause of the low pressure was continuous absorption from the subretinal space an explanation postulated by Beigelmann as early as 1929

On the assumption that such absorption from the subretinal space is a constant phenomenon one finds that many puzzling features of the operative treatment of retinal detachment can be explained in a simple manner

With respect to buckling operations one may conveniently start with an open rupture combined with average elevation (Fig 1) Assuming absorption

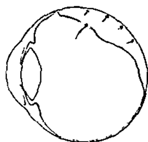


Fig 1

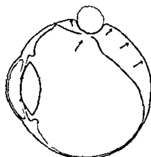


Fig 2

Fig 1 Fluid passing through the rupture prevents pressure decrease in the subretinal space

Fig 2 Blockage of the rupture by a scleral impression enables pressure reduction in the subretinal space and the relatively higher pressure in the vitreous presses the rupture margins against the bulge

ture When the elevation is shallow it is no doubt possible that the bulge might press against the margins of the rupture But to create true valve action the margins of the rupture must also be pressed against the bulge This requirement becomes more difficult to realize the deeper the elevation and hence the more difficult it becomes to reach the retinal rupture margins exactly The fact that it is possible to close the rupture in such cases also demonstrates that the bulge alone is not decisive and that *an additional, hitherto neglected force must be at work*

Schepens attributed the action of his encircling bulge to *reduced traction in vitreous filaments* adhering to retinal ruptures Such loss of tension would presumably facilitate contact but this theory does not explain why the effect should be more beneficial in front of than behind the bulge An open rupture behind the encircling bulge is disastrous ruptures in front of the bulge may at first remain open and then heal *per continuitatem* As long as this difference remains unexplained this theory cannot be said wholly to account for what happens in these interventions

It may be said in sum that the above theories more or less satisfactorily explain the establishment of contact between retina and choroid For a real contact however it is necessary to bring the elevation to disappear by closing the rupture and this requires pressure not only from the outside but also counter pressure from the other side of the retina In the following I shall discuss the role of pressure from the vitreous in buckling operations

This aspect of the problem almost unexpectedly came to my attention when I was treating a patient last year It was a case of retinal detachment treated with silicone injections The patient was a woman aged 61 with singularly massive heredity including a daughter with both eyes blind after detachment The patient s left eye is blind for the same reason In 1957 her right eye was operated on for cataract with good vision In August 1969 detachment occurred in this eye She wa operated on with buckling interventions three times but healing did not ensue She was sent to have silicone injections Before the sili cone injections the right eye could perceive hand movement temporally The anterior parts of the eye seemed normal except for a very distinct flare in the anterior chamber Aphakia The light path in the anterior chamber could be followed into the vitreous no structures visible in the vitreous An open rupture was situated slightly behind the equator at 9 o clock Marked hypotension

Fractionated silicone injections were administered through pars plana at 12 o clock As a rule when this technique is used it is possible to inject only 0 2 to 0 3 ml before there is a marked rise in intraocular pressure which how ever soon diminishes By giving injections on alternate days the vitreous space can little by little be filled but one should keep in mind the risk for undue

the subretinal space will be absorbed (Fig 3) Even if the passage is imperfectly blocked at first – as when the elevation is deep – there will nevertheless be a tendency to higher pressure in the vitreous and this difference will gradually become more pronounced the closer the margins of the rupture get to the bulge

This theory greatly facilitates our understanding of the action of the encircling interventions Take for example *Arruga s suture* If there is an open rupture the pressure difference between the subretinal space and the vitreous will be equalized Arruga s suture introduces a wedge shaped bulge behind the rupture (Fig 4) The flow of fluid between the vitreou and the posterior portion of the subretinal space is thereby impeded and the result will be that the pressure in the vitreous will now rise above that in the aforementioned part of the subretinal space which in turn will force the retina against the wedge shaped bulge (Fig 5) completely sealing off the space behind it whereupon the fluid will be absorbed rapidly On the other hand in front of the suture the elevation will often persist (Fig 6) as will be well known to any surgeon who has used this method However such an elevation is generally limited in area and can never be particularly deep and as a rule it heals *per continuitatem*

Summary

The significance of buckling operations in surgery for retinal detachment has been well documented but there exists no accepted explanation of how they work. The theory here presented regarding absorption from the subretinal space as the prime mover explains how blockage of the rupture by means of the buckling operations can be effective

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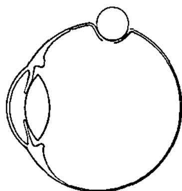


Fig 3

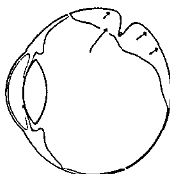


Fig 4

Fig 3 When the rupture has been blocked the fluid will be absorbed spontaneously
Fig 4 Arruga s suture creates a wedge shaped bulge which impedes the passage of fluid to the posterior portions of the subretinal space.

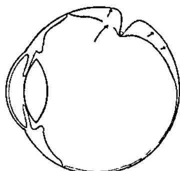


Fig 5

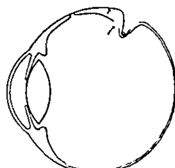


Fig 6

Fig 5 Pressure reduction in the subretinal space and corresponding increase in the vitreous forces the retina towards the scleral
Fig 6 Postoperatively a shallow elevation often persists in front of the suture

from the subretinal space one would expect the pressure in it to be lowered compared with the pressure in the vitreous But this development is cancelled out by passage *through the rupture and the elevation persists*

Now let a buckling intervention e g a *plombage operation* be made (Fig 2) Then the pathognomically important tedency to pressure equalization via the rupture will be blocked and the pressure in the subretinal space will eventually be somewhat lower than that in the vitreous The higher pressure in the vitreous will force the margins of the retinal rupture against the bulge and the fluid in

the subretinal space will be absorbed (Fig 3) Even if the passage is imperfectly blocked at first – as when the elevation is deep – there will nevertheless be a tendency to higher pressure in the vitreous and this difference will gradually become more pronounced the closer the margins of the rupture get to the bulge

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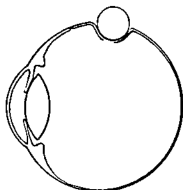


Fig 3

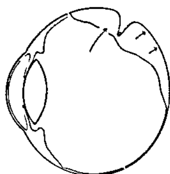


Fig 4

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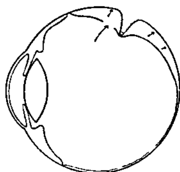


Fig 5

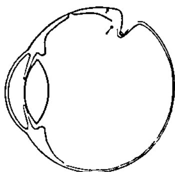


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Author s address
Professor B Rosengren Fridkullagatan 25 A 412 62 Goteborg Sweden

University of Bergen School of Medicine
Department of Ophthalmology
(Head Professor Torstein I Bertelsen M D)

THE SAGITTAL GROWTH OF THE EYE

IV Ultrasonic measurement of the axial length of the eye from birth to puberty

BY

JON S LARSEN

The length of the optic axis is measured ultrasonically by adding the values for the depth of the anterior chamber the length of the axial diameter of the lens and the length of the posterior segment (the vitreous)

The object of this study is to investigate the axial length of the eye in both sexes from birth to puberty and to throw light on the relationship between its components (the depth of the anterior chamber the axial diameter of the lens and the length of the vitreous) during the same period

A considerable number of measurements of the sagittal diameter of the eye have been made in enucleated eyes from newborns Most authors give mean values for the outer diameter of the bulb of between 17 and 18 mm (von Jaeger 1861 Merkel & Orr 1892 Halben 1900 Sorsby & Sheridan 1960) but mean values as low as 16 4 mm (Weiss 1897) have also been given Ultrasonic measurements of the axial length in living newborns were made by Gernet (1964) Luyckx (1966) and Grignolo & Rivara (1968) who all give mean values in the neighbourhood of 17 mm

Our knowledge of the longitudinal growth of the axis after birth is based mainly on studies made by Weiss (1897) Halben (1900) and Favoloro (1934) in

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Author s address
Professor B Rosengren Fridkullagatan 25 A 412 62 Goteborg Sweden

Table I (cont)

Age (years)	Sex	Sorsby et al (1961)	No of cases	Gernet & Hollwich (1968)	No of eyes	Grignolo & Rivara (1968)	No of cases
1 1½	M	–	–	20 44+ ±1 135 (0 2 years)	15	20 14+ (1 1½ years)	37
	F	–	–				
1½ 2	M	–	–			22 01+ (1½ 3 years)	35
	F	–	–				
2 3	M	–	–				
	F	–	–				
3 4	M	23 2	53				
	F	22 5	36				
4 5	M	23 2	52			22 78+ (4 5 years)	24
	F	22 7	50				
5 6	M	23 1	54				
	F	22 8	55				
6 7	M	23 4	51	21 47+ ±0 744 (0 12 years)	66	22.56+ (6 7 years)	26
	F	23 0	51				
7 8	M	23 6	60				
	F	23 1	55				
8 9	M	23 9	56			23 12+ (8 10 years)	39
	F	23 2	58				
9 10	M	23 8	47				
	F	23 2	52				
10 11	M	23 9	47				
	F	23 6	59				
11 12	M	24 0	53			–	–
	F	23 6	49			–	–
12 13	M	24 2	61			–	–
	F	23 6	57			–	–
13 14	M	24 1	54	–	–	–	–
	F	23 6	56	–	–	–	–
14 15	M	24 0	40	–	–	–	–
	F	23	75	–	–	–	–
Method		Phacometry		USG		USG	

Table 1

Earlier studies of the length of the sagittal axis during the growth period. Measurements *in vivo* show the *inner* axial length, *in vitro* measurements show the outer diameter (mm). M males, F females, + sex not given, USG ultrasonography

Age (years)	Sex	Weiss (1897)	No of eyes	*Halben* (1900)	No of eyes	Lavoloro (1934)	No of eyes
1–1½	M	19.9	2	21.5	2	–	–
	F	–	–	18.9	2		
1½–2	M	20.0	1			22.0+	?
	F	–	–	20.3	2		
2–3	M	–	–	19.25	2	–	–
	F	19.0	1	–	–		
3–4	M	21.5	1	–	–	23.0+	?
	F	–	–	–	–		
4–5	M	21.0	2	–	–	–	–
	F	–	–	–	–		
5–6	M	–	–	–	–	–	–
	F	–	–	18.9	2		
6–7	M	21.3	1+	–	–	–	–
	F	20.5	1	20.3	2		
7–8	M	21.9	4	–	–	24.0+	?
	F	21.0	1	–	–		
8–9	M	23.5	1	–	–	–	–
	F	21.0	1	–	–		
9–10	M	20.75	1	–	–	–	–
	F	–	–	22.75	2		
10–11	M	–	–	–	–	–	–
	F	–	–	–	–		
11–12	M	–	–	–	–	–	–
	F	–	–	–	–		
12–13	M	–	–	–	–	–	–
	F	–	–	–	–		
13–14	M	–	–	–	–	–	–
	F	21.75	1	–	–		
14–15	M	20.5	2	–	–	–	–
	F	–	–	–	–		
Method		Anatomical		Anatomical		Anatomical	

Age (years)	Sex	Sorsby et al (1961)	No of cases	Gernet & Hollwich (1968)	No of eyes	Grignolo & Rivara (1968)	No of cases
1–1½	M	–	–	20.44+ ±1.135 (0–2 years)	15	20.14+ (1–1½ years)	37
	F	–	–				
1½–2	M	–	–			22.01+ (1½–3 years)	35
	F	–	–				
2–3	M	–	–				
	F	–	–				
3–4	M	23.2	53				
	F	22.5	36				
4–5	M	23.9	[illegible]			22.78+ (4–5 years)	24
	F	22.7	50				
5–6	M	23.1	54				
	F	22.8	55				
6–7	M	23.4	51	21.47+ ±0.744 (0–12 years)	66	22.56+ (6–7 years)	26
	F	23.0	51				
7–8	M	23.6	60				
	F	23.1	[illegible]				
8–9	M	23.9	56			23.12+ (8–10 years)	39
	F	23.2	58				
9–10	M	23.8	47				
	F	23.2	[illegible]				
10–11	M	23.9	47				
	F	23.6	59				
11–12	M	24.0	53			–	–
	F	23.6	9			–	–
12–13	M	24.2	61			–	–
	F	23.6	57			–	–
13–14	M	24.1	54	–	–	–	–
	F	23.0	56	–	–	–	–
14–15	M	24.0	40	–	–	–	–
	F	23.7	75	–	–	–	–
Method		Phacometry		USG		USG	

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Earlier studies of the length of the sagittal axis during the growth period
Measurements *in vivo* show the inner axial length *in vitro* measurements show the outer* diameter (mm) M males F females + sex not given USC ultrasonography

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1 1½	M	19 9	2	21 5	2	–	–
	F	–	–	18 9	2		
1½ 2	M	20 0	1			22 0+	?
	F	–	–	20 3	2		
2 3	M	–	–	19 25	2	–	–
	F	19 0	1	–	–		
3 4	M	21 5	1	–	–	23 0+	?
	F	–	–	–	–		
4 5	M	21 0	2	–	–	–	–
	F	–	–	–	–		
5 6	M	–	–	–	–	–	–
	F	–	–	18 9	2		
6 7	M			–	–	–	–
		21 3	1+				
	F	20 5	1	20 3	2		
7 8	M	21 9	4	–	–	24 0+	?
	F	21 0	1	–	–		
8 9	M	23 5	1	–	–	–	–
	F	21 0	1	–	–		
9 10	M	20 75	1	–	–	–	–
	F	–	–	22 75	2		
10 11	M	–	–	–	–	–	–
	F	–	–	–	–		
11 12	M	–	–	–	–	–	–
	F	–	–	–	–		
12 13	M	–	–	–	–	–	–
	F	–	–	–	–		
13 14	M	–	–	–	–	–	–
	F	21 75	1	–	–		
14 15	M	20 5	2	–		–	–
	F	–	–	–			
Method		Anatomical		Anatomical		Anatomical	

Table II

Axial length in the eyes in this series. SD standard deviation. SE standard error

Length of axis mm	Days	Months		Years												
	1	6	9	1 2	2 3	3 4	4 5	5 6	6 7	7 8	8 9	9 10	10 11	11 12	12 13	13 14
15 50 15 99	2															
16 00 16 49	8															
16 50 16 99	27															
17 00 17 49	21															
17 50 17 99	5															
18 00 18 49	3	2														
18 50 18 99			2													
19 00 19 49			2		2											
19 50 19 99				2	14	2	2									
20 00 20 49				14	19	8	2		2					2		
20 50 20 99				10	46	21	6	4	4	2						
21 00 21 49				8	18	53	22	8	9	9	12	4		2		
21 50 21 99				2	19	12	35	29	21	20	12	6	10	4	4	
22 00 22 49						12	23	15	18	20	34	26	14	8	14	
22 50 22 99						2	10	4	6	15	38	36	22	26	10	10
23 00 23 49								4	2	4	4	6	10	6	12	8
23 50 23 99									2			2		4	14	6
24 00 24 49															2	
No of eyes	66	2	4	36	118	110	100	64	64	70	100	80	56	52	56	24
Mean	16 78	19 21	19 05	20 61	20 79	21 27	21 68	21 85	21 97	22 09	22 33	22 43	22 50	22 70	22 97	23 15
S D	0 51	–	–	0 47	0 61	0 55	0 55	0 59	0 71	0 62	0 51	0 47	0 47	0 52	0 71	0 38
S E	0 055	–	–	0 079	0 056	0 052	0 053	0 074	0 089	0 074	0 051	0 053	0 063	0 114	0 095	0 078

enucleated eyes and by Sorsby Benjamin & Sheridan (1961) Gernet & Hollwich (1968) and Grignolo & Rivara (1968) on living eyes The results of these studies are shown in Table I Although some of these measurement results show different rates of growth it seems that the growth of the eye is most rapid in the first 3 to 4 years of life the subsequent annual increase in length appearing to be slight

In measurement of the axis by ultrasonography (interferometer reading) Jansson (1963) gives the error of the method as 0 038 3 SD = ± 0 114 mm Nover & Grote (1965) give the error of the method as 0 2 per cent Nakajima & Kimura (1966) measured the axial length with ultrasound in 748 cases and compared the results with those of phacometry Good agreement was noted with a mean difference of –0 03 mm ± 1 20 Sorsby et al (1963) also found close agreement in the results obtained by ultrasonographic and phacometric methods with a mean difference in values for the axial length of +0 027 mm ± 0 31

Material and Method

The material and method have been described in detail in earlier publications (Larsen 1971 a b c) Only the main features will be repeated

The material includes 80 mature newborns 43 boys and 37 girls In the age group 6 months – 13 years 465 boys and 381 girls with normal eyes were examined Both eyes were examined in all subjects (1852 eyes) The age group 6 months – 7 years was examined under general anesthesia in connection with surgical treatment of otitis or tonsillitis With the exception of the newborns the examination was made under cycloplegia induced by Cyclogyl® 1 per cent The study includes only eyes with refractive values between + 5D and –5D Eyes with anisometropy greater than 2D were excluded The apparatus used for the biometric measurements was a Siemens Echo ophthalograph (Krautkrämer system) type USIP 10 and a 6 Mc/5 mm tranducer

The length of the optic axis (D_4) was determined by adding the values of the depth of the anterior chamber (D_1) the axial diameter of the lens (D) and the length of the vitreous (D_3) i e $D_4 = D_1 + D + D_3$ (The determination of D_1 D and D_3 has been described earlier Larsen 1971 a b c)

In addition to the examinations made in individuals in the growth period measurements of the right eye were made in 10 emmetropic men and in 10 emmetropic women aged 20 40 years to give a basis of comparison with the length of the optic axis during puberty

The precision of the measurements was determined by 10 different measurements of the right eye of an adult subject The results of these measurements gave the mean values 23 30 mm SD = ± 0 047 3 SD = ± 0 141 mm

Table III

Axial le gth in the pre nt female eric SD tanda d d viat on SL standa d e ror

Length of axis mm	Days	Months		Years													
	1 5	6	9	1 2	2 3	3 4	4 5	5 6	6 7	8	8 9	9 10	10 11	11 12	12 13	13 14
15 00 15 49	1															
15 50 15 99	7															
16 00 16 49	20															
16 50 16 99	30															
17 00 17 49	10															
17 50 17 99	6															
18 00 18 49		2														
18 50 18 99			2													
19 00 19 49				2												
19 50 19 99				6	11	4										
20 00 20 49				9	31	13	15	1	2							
20 50 20 99				5	32	36	18	15	12	6						
21 00 21 49					18	23	21	15	21	8	6	6	4	8	14	
21 50 21 99					10	12	8	12	20	12	10	10	8	14	6	
22 00 22 49					2	2	4	3	5	16	8	12	12	10	20	10
22 50 22 99									2	4	8	16	14	20	8	26
23 00 23 49										4		4		12	24	8
23 50 23 99													6	8		4
24 00 24 49									2						4	
No of eyes	74	2	2	22	104	90	66	46	64	50	32	48	44	72	76	48
Mean	16 40	18 21	18 66	20 15	20 72	20 96	21 03	21 24	21 51	21 48	22 05	22 19	22 17	22 50	22 53	22 66
S D	0 52	–	–	0 20	0 59	0 48	0 50	0 51	0 70	0 63	0 59	0 52	0 59	0 78	0 86	0 53
S E	0 060	–	–	0 043	0 058	0 051	0 062	0 075	0 088	0 089	0 104	0 075	0 089	0 092	0 099	0 076

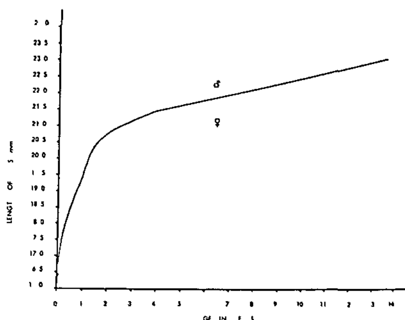


Fig 1
Growth curve (mean values) for the length of the optic axis

Results

Tables II and III show the axial length in the different year classes for boys and girls respectively During the first year and a half after birth the mean value increases from 16 78 to 20 61 mm in boys and from 16 40 to 20 15 mm in girls In the following 2 years the mean value increases by 0 7 0 8 mm in both sexes From the age of 3 years to the age of 8 years the axial length increases by approx 1 mm and subsequently by approx 0 8 mm in boys and 0 6 mm in girls *up to the age of 13 years At this age the mean value is 23 13 mm in boys* and 22 66 mm in girls By comparison the mean values in 10 emmetropic men aged 20 40 years was 23 16 and in 10 emmetropic women 22 68 mm Fig 1 shows the growth curve from birth to 13 years

In an earlier study (Larsen 1971 c) a sex linked difference in the length of the vitreous was found at birth and during the whole period of growth the difference being reflected in the different forms of refraction A similar relationship is also reflected in the length of the whole of the optic axis The difference in mean values between the two sexes was 0 38 mm in newborns in the other year groups from 0 26 to 0 46 mm cf Table IV In all age groups the difference was significant ($P < 0\ 01$)

The relationship between axial length and refraction was studied in infants in the age group 1 3 years (480 eyes) and in 12 year old girls (76 eyes) It was only in these groups that the dispersion in refraction (values between +5D and -5D cf tabular survey Larsen 1971 a Tables IV and V) was sufficiently great

Table V

Axial length (mean) in the different refraction states and the difference between sexes in the age group 1 3 years M myopia, E emmetropic H hypermetropia Test of significance Student T test

Sex		Age in years			Total			
		1 2	2 3	3 4	Mean	Differences	P values	No of eyes
Boys	M	20 78	21 32	21 53	21.33			[illegible]
	E	20 16	20 36	20 89	20 66	0.30 (EB EG)	0 01 < P < 0 05	86
	H	19 83	20 28	20 57	20 32			153
Girls	M	20 27	20 54	–	20 47			8
	E	–	20 18	20.54	20.36	0 19 (HB HG)	P < 0 01	106
	H	19 [illegible]4	20 12	20.38	20 13			102
Total	M	20 44	20 80	21.53	20 84	0 39	P < 0 01	28
	E	20 16	20 [illegible]5	20 [illegible]2	20 49	0 25	P < 0 01	192
	H	19 74	20 21	20 49	20 24			260

EB emmetropic boys EG emmetropic girls HB hypermetropic boys HG hypermetropic girls

to be capable of giving a realistic picture on statistical computation (The same year classe were used in illustrating the relationship between refraction and the depth of the anterior chamber and between refraction and the length of the vitreous Larsen 1971 a, c) Fig 2 shows the growth curve in the age group 1 3 years for the different forms of refraction As shown in Table V the mean value for myopic children in this age group is 0 39 mm greater than in emmetropes who again have a mean value 0 25 mm greater than hypermetropes The difference in mean value is significant ($P < 0\ 01$) The sex linked difference in axial length is also reflected in the different forms of refraction The mean value for hypermetropic and emmetropic boys is thus 0 2 0 3 mm higher than in girls with corresponding forms of refraction (cf Table V and Fig 2) The sex linked difference is significant ($P < 0\ 01$) in hypermetropes and probably significant ($0\ 01 < P < 0\ 05$) in emmetropes In this age group there were so few myopes that separate curves for boys and girls would not have given a true picture In older children (12 year old girls) the relationship between axial length (y) and refraction (x) is shown in Fig 3

Line of regression $y = 22\ 443 - 0\ 325\ x$ mm

$r = -0\ 824$

$sr = 0\ 065$

$P < 0\ 001$

Table IV

Axial length in age groups (mean values) and the difference between sexes *Test of significance* Student T test

	Sex	Age				
		Days 1 5	Years 1 2	2 6	7 9	10 13
Length of axis (mean) mm	Boys	16 78	21 11	21 42	22 28	22 70
	Girls	16 40	20 65	21 03	22 02	22 40
Differences mm		0 38	0 46	0 39	0 26	0 30
P values		P < 0 01	P < 0 01	P < 0 01	P < 0 01	P < 0 01
No of eyes	Boys	86	36	456	250	188
	Girls	74	22	370	130	240

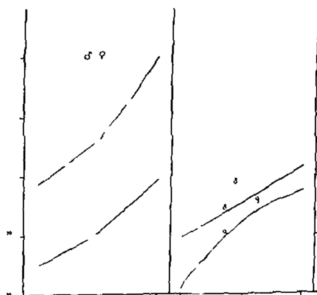


Fig 2

Growth in the different forms of refraction in the age group 1 3 years M myopia E emmetropia H hypermetropia

Table VI

Relative share of axial length during growth period represented by components expressed as percentage D1 depth of anterior chamber D1 + D2 length of anterior segment (corneal vertex – posterior pole of the lens) D3 length of vitreous

Age	Boys				Girls			
	No of eyes	D_1	D_1+D	D_3	No of eyes	D_1	D_1+D	D_3
Days								
1 5	86	14 1	37.5	62.5	[illegible]4	14 5	38 8	61 2
Years								
1 2	36	16 3	33 8	66 2	22	16 1	34 2	65 8
2 3	118	16 3	33.5	66.5	104	16 2	33 8	66 2
3 4	110	16.5	33.5	66.5	90	16 0	33 3	66 7
4 5	100	16 2	32 9	67 1	66	16 0	33 0	67 0
5 6	64	16 1	32 6	67 4	46	15 6	33 0	67 0
6 7	64	16 1	32 0	68 0	64	16 0	32.5	67.5
7 8	0	16.3	32 4	67 6	50	16 4	32 1	67 9
8 9	100	16 3	31 8	68 2	32	16.3	32 1	67 9
9 10	80	16 2	31 6	68 4	48	16 0	31 8	68 2
10 11	56	16 3	31 4	68 6	44	16 2	31 8	68 2
11 12	52	16 0	31.3	68 7	72	16 2	31 6	68 4
12 13	[illegible]6	16 2	30 9	69 1	[illegible]6	15 9	31 4	68 6
13 14	[illegible]4	16 0	30.5	69 5	48	16 0	31 2	68 8

Fig 4 gives a graphic survey for both sexes of the components of the optic axis and their magnitude in the individual year classes from birth to the age of 13 years and Table VI shows the percentual share of the axial length represented by these components in the different year classes As the table shows the depth of the anterior chamber represents slightly above 14 per cent of the axial length in newborns rising to approx 16 per cent at the age of one and a half years this relationship remaining more or less constant throughout the rest of the growth period to puberty At birth the distance from the corneal vertex to the posterior pole of the lens is approx 38 per cent (37 5 per cent in boys 38 8 per cent in girls) of the total axial length At the age of a year and a half it is approx 34 per cent of the optic axis and at 13 years 30 31 per cent The length of the vitreous however represents an increasing percentage of the length of the eye on increasing age from 62 5 per cent in newborn boys and 61 2

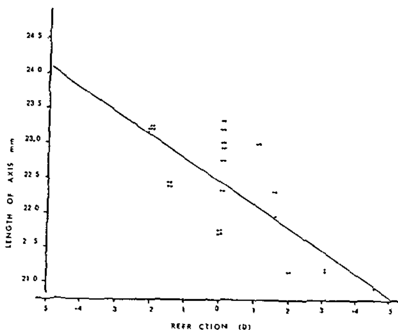


Fig 3

Correlation between length of axis and refraction girls aged 12 years (76 eyes) Regression line $y = 22\,445 - 0\,825\ x$ mm Correlation coefficient $r = -0\,824$

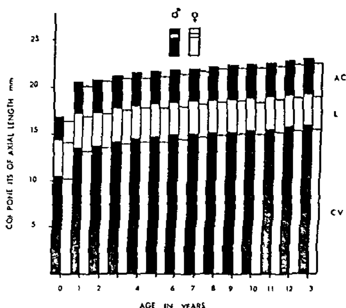


Fig 4

Relation between the different components of the axis during the growth period AC depth of anterior chamber L axial thickness of lens CV length of vitreous

In living eyes the axial length was measured phacometrically by Sorsby et al (1961) from the 4th year of life to the end of the growth period As it appears from Table I the values given are larger than those found for corresponding year classes in the present study Gernet & Hollwich (1968) appear to be the only authors who have made in vivo measurements of *axial length during the whole* growth period from birth to 12 year (66 emmetropic eyes) They found that the axis increased in length from approx 17 mm in newborns to rather more than 23 mm in 12 year olds i e values similar to those found for corresponding age groups in the present study

Summary

The length of the optic axis was measured by ultrasonography in 926 children (1852 eyes) 80 newborns and 846 aged 6 months to 13 years From birth to 13 years the mean value increased from 16 78 to 23 15 mm in boys and from 16 40 to 22 66 mm in girls Compared with the measurements made in emmetropic adults (20 40 years) the optic axis thus appears to have reached full or almost full length The growth of the eye can be divided into 3 growth phases A rapid postnatal phase with an increase in length of 3 7 3 8 mm in the first year and a half of life a slower infantile phase lasting to the age of 5 years with an increase in length of 1 1 1 2 mm followed by a slow juvenile phase up to the age of 13 years with an increase of 1 3 1 4 mm

During the entire growth period there is a sex linked difference in axial length the values being approx 0 3 0 4 mm higher in boys

The relationship between refraction and axial length reflects that earlier found (Larsen 1971 a c) between the depth of the anterior chamber and the length of the vitreous – a *negative correlation established* by the age of one year

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per cent in newborn girls to 66 2 and 65 8 per cent *respectively, at the age of a* year and a half and to approx 69 per cent in both sexes at 13 years

Discussion

According to the measurement results in this study the longitudinal growth of the optic axis can be divided into 3 growth periods A rapid post natal phase with an increase in length of 3 7 3 8 mm in the first year and a half, followed by a slower infantile phase from the 2nd to the 5th year of life with an increase in length of *1 1 1 2 mm and finally by a slow juvenile phase lasting* until the age of 13 years with an increase of 1 3 1 4 mm The optic axis has then reached the values found in emmetropic adults It seems that the longitudinal growth terminates at the age of 13 or is minimal after this age This accords with the results of earlier studies (Sorsby et al 1961, Gernet & Hollwich 1968)

It is well known that there is a sex linked difference in the axial length in adults with larger values in men than in women (Jansson 1963 Gernet 1964 Nover & Grote 1965) A corresponding sex linked difference in axial length was found to be present in this study during the entire growth period values in boys *being on the average 0 3 0 4 mm larger than in girls The question* of whether refraction which was not determined in the newborns may have affected the values in the two sexes cannot be assessed It is however improbable that a difference in ocular refraction in a haphazardly chosen material such as this would have been of a magnitude capable of having a material effect on the measurement results It therefore seems probable that the sex linked difference in results is real This would seem to be corroborated by the fact that the difference in measurement values remains fairly constant in the growth period the relative rate of growth being thus the same in both sexes

In the case of newborns it has been stated that there is no fixed relationship between axial length and refraction (Gernet 1964 Luyckx 1966) The present study shows that a negative correlation between these components is developed early in the postnatal period and at any rate from the age of one year appears to be fully established

When the results in newborns in the present study are compared with measurements made on enucleated eyes they are found to accord well with most studies (von Jaeger 1861 Merkel & Orr 1892 Halben 1900 Sorsby & Sheridan 1960) if the thickness of the posterior wall is taken into account The relatively few studies made in enucleated eyes during the period of growth describe somewhat diverging rates This is probably due to the materials being small and to the lack of uniformity in the methods used in preparing the eyes for measurement

Department of Ophthalmology Kommunehospitalet
Copenhagen Denmark
(Heads P Brændstrup M S Norn & K Norskov)

IRIS PIGMENT DEFECTS IN NORMALS

BY

M S NORN

Abstract

Defects of the iris pigment layer have been studied in normal eyes by means of transpupillary transillumination according to Abrams Defects were detected near the pupil and in the pupillary ruff

Such defects were seen in none of the normal subjects aged under 45 but were increasingly frequent in the older age classes (5 per cent irides with pig ment layer defects and 10 per cent with pupillary ruff defects in the age class of 45–50 against 62 and 56 per cent respectively among the normals aged over 80) The defects were most often found infero nasally The defects near the pupil consisted in half of the cases of few punctate holes and in the other half of more than five holes of larger holes or confluent holes

A knowledge of such defects in normals is required before it is possible to assess whether defects in a given patient may be signs of a pathological condition (uveitis *acute glaucoma* injury etc) or merely indicate a physiological *age determined* wear and tear within the pupillary region

In addition to the defects described above transparency within a sector inferiorly in the iris was seen in 4 per cent of the normal series This pheno

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Department of Ophthalmology Kommunehospitalet
Copenhagen Denmark
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A knowledge of such defects in normals is required before it is possible to *assess whether defects in a given patient may be signs of a pathological con*dition (uveitis acute glaucoma injury etc) or merely indicate a physiological age *determined wear and tear within the pupillary region*

In addition to the defects described above, transparency within a sector inferiorly *in the iris was seen in 4 per cent of the normal series This pheno*

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menon may perhaps, be interpreted as an abortive coloboma of the posterior lamina of the iris

Key Words Iris – pigment – defects – transillumination – transparence – Iris ruffs – normals

Defects of the pigment layer of the iris are a well known phenomenon following grave eye injuries iritis acute glaucoma and in association with albinism

It is not evident from the literature whether defects may also be found in the pigment layer of normal eyes, or whether detection of such defects indicates presence of pathological processes

Larsson & Österlind (1944) have subjected defects of the pupillary ruff of 14 cataractous patients to histological examination

Abrams (1964 a b) has described punctate defects in an inferior sector of the iris as a phenomenon seen very occasionally in normals

It is well-known that also in normals pigment may be present on the trabecular network on the posterior corneal surface and on the anterior surface of the lens These pigment granules must be supposed to originate from the iris pigment layer The physiological movements of the pupil may presumably give rise to pigment defects These being minute they may possibly regenerate The pigmented epithelium of the iris is however fairly unable to regenerate (Norn 1968)

An exact knowledge of the iris pigment layer in normal eyes is required to be able to assess defects of this layer in pathological states The object of the present study has been such a mapping of possible pigment defects in a series of normal eyes

Method

By ordinary slit lamp examination (Haag Streit 900) I studied the iris ruff in direct light and recorded possible defects

Defects of the pigmented epithelium of the iris were observed by transpupillary transillumination according to Abrams and recorded The slit lamp light beam was narrowed to scarcely pupil width The light beam was directed through the pupil parallel with the axis of the microscope (The arm of the slit lamp was set at zero) The patient fixed the light beam The rays were focused on the pigment layer (i e on the pupillary ruff or the anterior surface of the lens) The examination was made in half light The pupil shone red owing to reflected light from the fundus Iris pigment defects if present were

seen as luminous dots or areas on a dark background The examination was repeated from another angle to obtain optimum conditions (The corneal reflex may interfere The best angle is often 10–20 degrees towards the temporal side)

Material

A total of 618 irides of 309 subjects were examined The ages ranged from 8 to 91 The subjects were patients seen in ophthalmic practice or in the ophthalmic out patient clinic They had been referred for routine examination or had had conjunctival complaints or minor refractive anomalies Conditions that might be conceived to cause iris defects were ruled out

Result

Iris pigment defects may be naturally classified in three groups one comprises punctate or larger defects round the pupil and one defects of the pupillary ruff

The third group comprises the sector formed transparency inferiorly in the iris

Defects Near the Pupil

Defects of the iris pigment layer near the pupil may be graduated according to severity from 1 to 4 (Fig 1)

Few and small holes from 20 to 100 μ round the pupil represent grade 1 and presence of more than five holes of the same order grade 2 If larger holes up to 1/2 mm in size are present as well the defect is of grade 3 Finally combination with confluent defects up to 1/2 mm broad represents grade 4

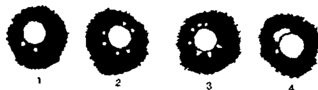
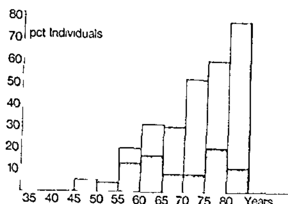


Fig 1
Iris epithelium defects near the pupil Type 1 Less than five minute defects Type 2 five or more minute defects Type larger defects as well Type 4 confluent defect



Graph 1

Defects near the pupil in the iris pigment layer of normals

Dependence on age

Abscissa Ages of the subjects (five year age groups)

Ordinate Number of subjects (in per cent) who had iris defects Lower curve subjects with defects of one iris only Upper curve subjects with defects of one or both irides

Grade 1 was found in 51 per cent of the irides showing defects near the pupil while grade 2 was noticed in 25 per cent grade 3 in 6 per cent and grade 4 in 18 per cent

Few and small holes (grade 1) were thus the most frequent finding

In the present normal series none of the irides presented loss of pigment outside the central one fourth of the iris ruff (except the inferior sector formed defects see below)

Table I

Age	Number of irides	Defects near pupil %	Pupillary ruff defects %	Sector formed transparency %
<45	188	0	0	2
45–49	42	5	12	5
50–54	46	4	20	4
55–59	60	13	18	7
60–64	72	31	28	11
65–69	74	26	30	0
70–74	50	48	42	4
75–79	50	50	46	4
>80	36	72	56	0

Defects of the iris pigment layer in 309 normal subjects Dependence on age

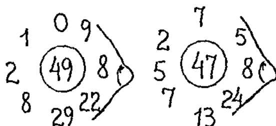


Fig 9

Sites of iris epithelium defects To the left schedule of defects near the pupil of which 49 were distributed over the whole circumference To the right pupillary ruff defects A total of 1 8 irides of each type

Finding of defects near the pupil in normal eyes is age determined Graph 1 illustrates the age incidence. The series under review was divided into five year age groups No defects were demonstrated in normals under the age of 45 The number of subjects with defects rose gradually in the following five year age groups from 5 per cent in that of 45–50 to 78 per cent in the group aged over 80

In a scant one third of the cases defects were limited to one eye The lower curve shows the incidence of unilateral cases The difference between the two curves represents the bilateral cases which rose considerably in number with increasing age

Table I shows the incidence of iris defects estimated by the number of eyes examined Right and left eyes were equally represented (20 7 per cent had defects of the right iris and likewise 20 7 per cent of the left)

No sex difference was demonstrable (21 per cent females and 19 per cent males no difference after correction for age)

Fig 2 illustrates the sites of the defects These were often equally distributed over the whole circumference of the pupil (49 cases) The mainly localized defects were most often concentrated inferiorly and infero nasally

Pupillary Ruff Defects

The pupillary ruff may be regarded as a projecting part of the pigment layer of the iris

Holes in this layer may be continuous with defects of the pupillary ruff Fig 3 shows instances of such continuity between pigmentary ruff defects and iris pigment defects near the pupil

In Fig 3 C the pupillary ruff was judged to be normal on slit lamp examination while the defect of the iris was plainly visible on transillumination Fig 3 D shows concurrent defects of pupillary ruff and iris

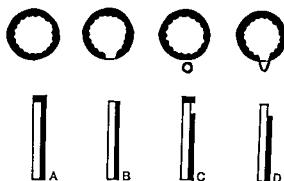


Fig 3

Relation between pupillary ruff defect and defects near the pupil Upper row front view Lower row imaginary cross section through the iris from the lower pupillary border A normal iris with no defect B pupillary ruff defect C iris pigment defect near the pupil D confluent pupillary ruff defect and pigment layer defect

Defects of the pupillary ruff consist in distinct notches or interrupted continuity of the otherwise regular undulating black ruff The defects may be spread round the entire pupillary region or be more localized The latter defects are most often concentrated infero nasally nasally or inferiorly (Fig 2)

Table I illustrates the age dependence of the pupillary ruff defects No defects were seen in subjects under the age of 45 The incidence was seen to rise gradually with increasing age from 12 per cent of the eyes within the age class of 45–49 to 56 per cent in the group aged over 80

There was no difference in incidence between the two eyes (20 1 per cent of right eyes and 21 3 per cent of left eyes) Neither was any sex difference demonstrated (21 1 per cent male eyes with defects and 20 6 per cent female eyes)

In two thirds of the cases pigment layer defects near the pupil were also found In the remaining one third the pupillary ruff defect was an isolated phenomenon

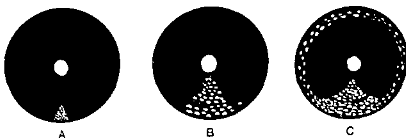


Fig 4

Sector formed iris pigment defect Three different types

Sector Formed Defect Inferiorly in the Iris

Abrams has described occurrence in normals of a transparent sector formed region inferiorly in the pigmentary layer of the iris

Figs 4 A and B show the most frequent findings innumerable minute holes within a well defined wedge shaped region having its apex close to the pupil and its base in the direction of the periphery of the iris between 5 and 7 o clock

Fig 4 C shows the only case in which defects were also found to extend along the whole periphery The patient was not an albino

In one case the equator of the lens was just visible through the pigment loss system

A single case was abortive in as far as no more than three or four holes within the sector formed iris region were found inferiorly in the two eyes

The phenomenon described above was in all cases present in both eyes It was seen in a total of 12 subjects of the present series (4 per cent) in three combined with iris pigment defect elsewhere and in nine as an isolated finding

The incidence was independent of age (Table I) The youngest subject was 19 years old and the oldest 79 No sex difference was noticed (3 per cent females and 4 per cent males)

Comments

Defects of the pupillary ruff may be difficult to detect in patients with a highly pigmented brown anterior surface of the iris In a light iris on the other hand the ruff is plainly visible as a dark band The figures stated for incidence of pigmentary ruff defects must therefore be regarded as minimum values

Defects of the iris pigment epithelium are easily demonstrated by Abrams s method Even defects as small as 20 μ in diameter are seen as luminous dots on a black background The statements of incidence must be regarded as reliable

In the series under review no defects were detectable in the iris pigment layer near the pupil nor in the pupillary ruff of normal individuals aged under 45 This is an important observation, because it means that such defects when found in patients below the age of 45 are to be regarded as pathological suggesting that the patients has or has had uveitis (Norn, to be published) acute glaucoma (Vorting to be published) injuries (Norn 1969) or the like

Defects near the pupil or in the pupillary ruff may be seen in normals after the age of 45 rising in number with increasing age The most likely explana

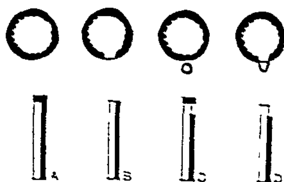


Fig. 8

Relation between pupillary ruff defects and defects near the pupil. Upper row: frontal view. Lower row: imaginary cross section through the iris from the lower pupillary border. A: normal iris with no defects. B: pupillary ruff defect. C: iris pigment defect near the pupil. D: confluent pupillary ruff defect and pigment layer defect.

Defects of the pupillary ruff consist of distinct notches or interrupted continuity of the otherwise regular undulating black ruff. The defects may be spread around the entire pupillary region or be more localized. The latter defects are most often concentrated inferonasally, nasally or inferiorly (Fig. 2).

Table I illustrates the age-dependence of the pupillary ruff defects. No defects were seen in subjects under the age of [illegible]. The incidence was seen to rise gradually with increasing age, from 12 per cent of the eyes within the age-class [illegible]5–49 to 5[illegible] per cent in the group aged over [illegible]0.

There was no difference in incidence between the two eyes (20.1 per cent of right eyes and 21.8 per cent of left eyes). Neither was any sex difference demonstrated (21.1 per cent male eyes with defects and 21.[illegible] per cent female eyes).

In two-thirds of the cases pigment layer defects near the pupil were also found. In the remaining one-third the pupillary ruff defect was an isolated phenomenon.



Fig. 9

[illegible] Three [illegible]

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Comments

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Defects near the pupil or in the pupillary ruff may be seen in normals after the age of 45 rising in number with increasing age. The most likely explana

tion of this finding is that the physiological pupillary movements expose the iris pigment epithelium to wear. This results in a destruction of the epithelial cells with which the regeneration cannot keep pace.

The process may be expressed as the "butterfly scales" becoming worn off the iris in the course of years.

Accordingly, observation of minor defects in an elderly individual need not indicate presence or previous existence of a pathological process, but may be an age determined phenomenon.

Defects near the pupil in the iris pigment layer and defects of the pupillary ruff are subject to the same age variations in normals. Further, they are present in the same region and may be confined to one eye. These two forms of pigment epithelium defects seem to be related. They are probably both due to pupillary movements in normal elderly individuals.

Unlike the above abnormalities, the sector formed defect inferiorly in the iris of normal eyes is always bilateral. It is most often the sole defect of the pigment epithelium in the individual concerned and is independent of age. In other words, the sector formed defect differs markedly from the two other types.

The sector formed defect may, perhaps, be regarded as an abortive form of congenital coloboma, its extension inferiorly in the iris corresponding to that of congenital coloboma.

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From the Department of Ophthalmology
Kommunehospitalet
Copenhagen Denmark
(Heads P Brændstrup M S Norn & K Norskov)

IRIS PIGMENT DEFECTS IN UVEITIS

BY

M S NORN

Abstract

Series of 90 eyes affected with uveitis and 110 eyes with simple glaucoma have been examined by transpupillary transillumination according to Abrams

In the series with uveitis defects were found in the iris pigment layer and in the pupillary ruff whereas in the simple glaucoma series the conditions were as in normals

The incidence and sizes of defects in association with uveitis were seen to increase with rising numbers of attacks Such factors as type of uveitis and age of the patients on the other hand are of secondary importance.

In patients under 45 years of age finding of even minute defects must be regarded as pathological whereas in older patients only larger possibly confluent defects can be declared definitely pathological

Key word Defects iris pigment pupillary ruff uveitis iritis glaucoma simplex

In cases of uveitis the inflammatory reaction and the subsequent cicatrisation cause disorders within the pupillary region Such may be synechiae atrophies in the anterior iris layer connective tissue production invasion of vessels – in

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some instances across the anterior lens surface – depositing of pigment epithelium flakes on the anterior lens surface and pupillary ruff defects

In the slit lamp the disorders constitute a polymorphous three dimensional picture, most plainly visible after dilation of the pupil However a polymorphous picture is likewise seen in normal eyes (iris crypts trabeculae vessels naevi and varying shades of colour)

In cases of uveitis iris pigment defects near the pupil may be seen as well Such defects are best disclosed by transpupillary transillumination according to Abrams in the slit lamp where a beam slightly narrower than the pupil is directed through the latter, parallel with the axes of observation of examiner and examined (Abrams)

Using this technique pigment layer defects even as small as 20 μ are visible as luminous red dots or areas on a black background The picture is monotonous two dimensional impossible to misinterpret and dilation of the pupil is unnecessary

In a previous paper I reported that also pigment defects may be found in the eyes of elderly normal individuals The present investigation aimed at throwing light on the incidence of defects in association with uveitis compared with that in a normal series Can we draw any conclusions in the individual cases in which such defects are found?

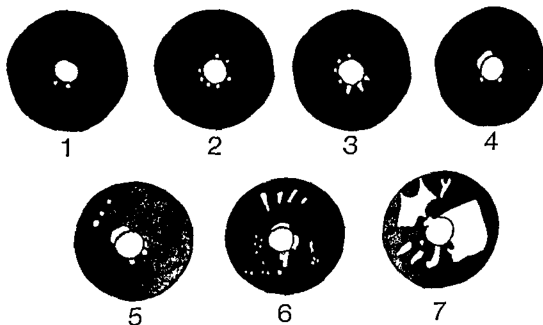


Fig 1
Defects in the iris pigment layer in uveitis Grades 1 – 7

Present Investigations

Method and Material

The transpupillary transillumination was performed through a Haag Streit slit lamp no 900 as described previously (Norn 1971) The series examined comprised 40 summoned patients These were the patients with the greatest number of relapses (more than five attacks) in a previously reported series of 449 uveitis patients (Norn 1969)

The group was supplemented by 25 consecutive non selected uveitis patients The uveitis material comprised a total of 90 eyes Another ten uveitis affected eyes were ruled out (owing to iridectomy or enucleation) A series of 618 normal eyes (Norn 1971) and one of 110 eyes with simple glaucoma are available for comparison

Iris Pigment Defects Near the Pupil

The observed defects (Fig 1) may be classified according to size and site in the following seven groups

Few minute defects round the pupil are characterized as grade 1 and presence of not less than five holes as grade 2 Defects comprising larger holes as well are of grade 3 while confluent defects constitute grade 4 Defects within grades 1 to 4 are confined to the central one fourth of the iris width

Cases of grade 5 also present minor defects peripheral to this region and cases of grade 6 considerable defects also peripherally Finally grade 7 represents maximum transparency also peripherally

Table I shows the uveitis material grouped on the basis of the above seven grades compared with the normal material It is seen that defects extending beyond the central one fourth of the iris only occurred in the uveitis material

Table I

Grade of defect	0	1	2	3	4	5	6	
Uveitis	3?	10	11	11	21	7	6	9
Normal eyes	9	11	[illegible]	1	4	0	0	0

Iris pigment defects in 90 uveitis affected eyes compared with 618 normal eyes Distribution of the defects in the two materials according to severity of grades 1 to 7 cf Fig 1 The figures indicate percentage of uveitis material and normal material respectively

some instances across the anterior lens surface – depositing of pigment epi thelium flakes on the anterior lens surface and pupillary ruff defects

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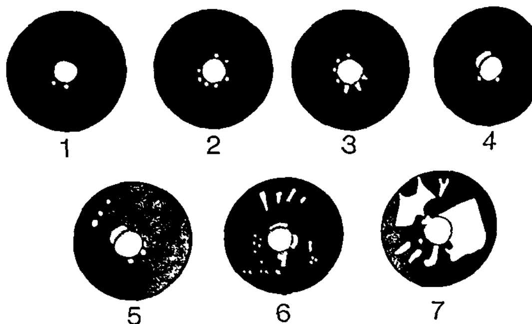


Fig 1

Defects in the iris pigment layer in uveitis Grades 1 – 7

Table III

Age	No of eyes			Iris pigment defect (%)		
	uveitis	normal	glaucoma	uveitis	normal	glaucoma
<20	0	78	0		0	
20–29	6	38	0	33	0	
30-39	9	32	0	56	0	
40–49	21	82	0	62	2	
50–59	26	106	14	73	9	14
60–69	25	146	78	80	28	18
70–79	3	100	44	100	49	50
>80	0	36	24		72	54

Incidence of iris pigment defects in uveitis affected eyes normal eyes and eyes with simple glaucoma calculated for 10 year age groups

Age Incidence

Table III illustrates that the incidence of uveitis affected eyes with associated defects rises with increasing age. This observation may however be due to the likewise rising number of relapses with increasing age Within the individual 10 year age groups the incidence of iris defects is seen to rise with increasing numbers of attacks Age thus seems to be a factor of secondary importance at most

No sex difference was demonstrable

Pupillary Ruff Defects

Defects in the pupillary ruff often coincide with iris pigment defects Pupillary ruff defects were noticed in 58 per cent of the uveitis material in 3 per cent as the sole defect The incidence of pupillary ruff defects rises with increasing number of relapses (Table II) but seems to be independent of the uveitis type and the patient s age

Simple Glaucoma

The iris pigment defects described in cases of uveitis might be conceived to be due to the mobilization of the pupil induced by treatment with mydriatics

Table II

No of attacks	No of eyes	Iris trans parency %	Transillumina tion grade mean	Pupillary ruff defect %
in first	3	0	0	0
1–2	24	33	0 71	29
3–5	23	65	2 09	89
6–10	34	94	3 50	88
11–20	6	100	4 17	100

Iris pigment epithelium defect in cases of uveitis Dependence on number of uveitis attacks a total of 90 eyes

not in normal eyes The highest grades of defects occurred almost exclusively among uveitis cases whereas the lowest were again seen among normal eyes.

Defects were detected in 68 per cent of 90 uveitis affected eyes against 21 per cent of 618 normal eyes The difference is highly significant ($p < 0\ 001$)

Recurrence Rate

Table II shows that the incidence of uveitis affected eyes with defects is higher the larger the number of uveitis attacks The difference is statistically significant The figures indicate that a single or few attacks need not give defects but that a series of attacks exposes the pigment epithelium to such wear that a possible regeneration cannot keep pace with the destruction

Uveitis Types

The material was devided into the following diagnostic groups acute fibrinous iritis subacute non fibrinous iritis nodular iritis central choroiditis and peripheral choroiditis

A calculation of the percentage number of irides with defects and of the average transillumination grade suggested that defects are most frequent and most pronounced in cases of acute and subacute iritis and least so though by no means rare in cases of posterior uveitis

The difference is possibly accountable for by the fact that acute fibrinous and subacute iritis are liable to the greatest number of relapses (*Norn 1969*) It is remarkable that posterior uveitis often is associated with iris defects Evidently secondary affection of the iris is so pronounced as to result in defects within this group too

place during the first attacks and proper defects develop and increase in size during the subsequent relapses

It is remarkable that considerable pigment defects have been detected in cases of posterior uveitis with no apparent associated anterior uveitis It is therefore to be supposed that even a minor secondary affection of the anterior ection may on repeated relapses give defects in the iris pigment layer

On seeing a patient with iris pigment defects near the pupil one may draw the following *conclusions* on the basis of the present and previous studies *(Norn 1971)*

If the patient is under 45 years of age the finding is pathological If older and the defects are fairly large perhaps even confluent the finding is likely to be pathological If the defect extends beyond the central one fourth of the iris the finding is *definitely* pathological

The pathologic l finding suggests that the patients has or has had uveitis Other pathological conditions must however also be considered (injuries acute glaucoma)

Absence of iris pigment defects suggests that the patient may have had uveitis but without several relapses (After one or two attacks 67 per cent had no defects after 6–10 attacks only 6 per cent)

On the basis of these conclusions it seems reasonable to employ transpupil lary transillumination according to Abrams in cases suspected of present or previous uveitis (cases with a vague past history rheumatic patients – as an aid in observation for spondylarthritis anchylopoietica Bechterew Behcet s syndrome Reiter s syndrome – and in cases of casualty and disablement state ments)

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I therefore studied a group of patients who likewise had received pupil mobilizing treatment This group comprised 57 patients (110 eyes) affected with simple glaucoma They had all been treated with miotics and 15 also with 1 % epinephrine The mean period of treatment had been 6 8 years

Table III shows the incidence of iris pigment defects in association with simple glaucoma to be the same as among normal eyes The same is true of pupillary ruff defects

Pigment cysts within the pupillary region were found in two patients, both treated with echothiophate iodide (Phospholine iodide) Altogether three patients had been treated with this miotic the others with pilocarpine physostigmine or mintacol

Comments

The uveitis material under review is dominated by cases with particularly many relapses 40 out of 65 patients constituting a selected group The incidence and extent of iris pigment defects is therefore supposed to be somewhat less in a purely consecutive series where the average recurrence rate is lower

The investigation gave results indicating that pigment defects depend on the number of relapses and that this factor seems to be more important than the type of uveitis and the patient s age

The present study thus left the impression that the repeated wear to which the pigment epithelium is exposed is of decisive importance whereas the individual violent attack of inflammation within the pupillary region plays an inferior role

How do pigment epithelium defects arise in cases of uveitis?

A man aged 54 presented no iris pigment defects in relation to an untreated first attack of acute fibrinous iritis Twenty minutes after the first pupil dilating treatment seven holes of different sizes were seen scattered in both nasal quadrants of the iris (grade 3 defect) and minor synechiae in the same region The defects developed during the mydriatic treatment

The series of glaucomatous eyes on the other hand showed that gymnastic exercises of the pupil by treatment with miotics are unable to provoke defects Note that the material comprised simple glaucoma only but not acute or prodromal glaucoma

The defects seen in cases of uveitis may be interpreted as a consequence of the combination of mydriatics and a tendency to synechiae Dilation of the pupil causes detachment of parts of the pigment epithelium which adheres to the anterior lens surface Local detachment of the pigment epithelium takes

An intraocular pseudotumour is any pathological intraocular process simulating a neoplasm It is a clinical descriptive entity but histopathologically a heterogenous group leading its investigators through large areas of ophthalmic pathology

In adults a variety of lesions mainly vascular play a part in the differential diagnosis of malignant choroidal melanoma and could also be designated as pseudotumours However we use the term in the present publication for a group of diseases simulating retinoblastoma i e corresponding to the old unfortunate term pseudoglioma We prefer to use the adjective intraocular and not retinal although the majority of these cases are retinal because some lesions are primarily choroidal and/or vitreal with secondary retinal changes

The aim of the present study was to correlate the clinical and histopathological aspects of such cases in Denmark over a 25 year period and in addition to make a comparison between these benign pseudotumours and the malignant retinoblastoma The material of retinoblastoma consisting of 69 cases used as reference has previously been published (Jensen 1965)

Material and Methods

In the Ophthalmic Pathology Laboratory a total of 357 children (up to 15 years of age) were filed as having been enucleated in the period 1942–1966 A total of 57 were filed with the diagnosis of intraocular pseudotumour

All foreign cases and all autopsy eyes where a pseudotumour was incidentally found had already been eliminated Lack of sufficient clinical and/or histopathological material reduced the series to a total of 45 The Danish population averaged 4 1 million over the period considered

All pertinent clinical data were procured and all sections of enucleated eyeballs reexamined Where necessary new sections in some cases serial sections and additional stainings were made

Results

Histopathology

Since the histopathological diagnosis in several cases of the older part of the material was pseudotumour exclusively it has been an aim in itself to put the cases into present day morphological groups and where possible into etiological groups The 45 patients in four main groups with their subgroups are

The Ophthalmic Pathology Laboratory and the Ophthalmic Tumour Centre (Head S Ry Andersen) University of Copenhagen Copenhagen Denmark

INTRAOCULAR PSEUDOTUMOURS IN DENMARK

A clinical and histopathological analysis and correlation of cases in children from 1942 to 1966

BY

O A JENSEN & J KLEENER

Abstract

A histopathological series of 45 children with intraocular pseudotumours in Denmark from 1942 to 1966 was studied The number of eyes examined was 50 The average population was 4 1 million A clinical and histo pathological correlation between these cases and a previously published series of 69 patients with retinoblastomas was undertaken

In about two thirds of the total material the clinical diagnosis was retinoblastoma and in the remainder a pseudotumour In the first of these groups just under half were cases of Coats s disease which was also the most frequent lesion in the total material Next in frequency were inflam matory lesions and malformations

Various clinical and histopathological aspects such as sex and age location past history general condition signs and symptoms are analysed indicative of the benign lesions or the malignant tumour It is concluded that it is the sum of many parameters and the experience of the clinician which may determine the correct diagnosis and that it is always wise to enucleate a useless eye The omnibus item pseudotumour should be re placed to the greatest possible extent by a pathogenetical diagnosis

Key words histopathology – intraocular pseudotumours – children – Denmark

This work was aided by a grant from the foundation established by P Th Rasmussen and his wife Alma Rasmussen administrated by the Danish Association of the Blind

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the retina while the other was suspected of being parasitic because of an abundant eosinophilic infiltration of the retina

All the eyeballs had a normal size apart from nine six of which were microphthalmic (all belonging to the group of malformations) and two buphthalmic (Coats's disease 1 septic endophthalmitis 1) One eye with endophthalmitis was phthisical Cataract was found in a little more than one third, with an even distribution over the groups Secondary retinal detachment was seen in a little more than half the cases also within all the groups

Dysplastic changes of the retina as a secondary phenomenon were observed in three eyes with inflammation and one with Coats's disease all in patients under two years of age Calcifications and ossifications appeared in four cases mainly in processes of long standing

Clinical aspects

The distribution of the cases over the 25 year period was uniform at about two cases a year apart from the last two years when no case appeared The Ophthalmic Tumour Clinic at the Ophthalmic Laboratory was established in 1964 The coordinated efforts of this centre and the referring clinical departments have perhaps reduced the number of eyes enucleated based on the vague diagnosis of pseudotumour

In about two thirds of the total material (28 patients) the clinical diagnosis was retinoblastoma and in the remainder (17 patients) a pseudotumour was considered most probable but enucleation was performed since a malignant tumour could not be ruled out Only in two cases was pain the main cause of enucleation

In the first of these groups (clinical diagnosis retinoblastoma) just under half were cases of Coats's disease while in the other group (clinical diagnosis pseudotumour) just under half were cases of inflammation Vice versa in our files there are six cases of retinoblastoma where the clinical diagnosis was a pseudotumour

Sex and age

The sex and age distribution is shown in Fig 1 Males number 26 and females 19 but in the cases of Coats's disease males were double the number of females (11 males 5 females) All the three cases of congenital dysplasia of the retina were girls The highest number of cases was found within the first three years of life as was the case in the retinoblastomas but although 80 per cent of the retinoblastomas were below three years of age at the time of treatment only 73 per cent of the pseudotumours were of that age The youngest patient in the retinoblastoma material was one month and the oldest 9 years among the pseudotumours the corresponding ages were two months and 12 years The

Table I
Histopathological diagnoses in 45 children with pseudotumour in Denmark 1942–1966

Main Group	Subgroup	Number	Total number
Vascular lesions	Coats s disease ,	9	16
	Coats s disease ?	7	
Inflammations	Septic endophthalmitis	4	
	Toxoplasmosis	3	
	Parasitic inflam ?	2	
	Chronic uveitis	2	
	Tuberculosis	1	
	Subchronic endophthalmitis	1	
	Panophthalmitis	1	
			14
Malformations	Congenital dysplasia of *retina*	3	
	Persistent hyaloid artery	2	
	Tuberous sclerosis	2	
	Norrie s disease	2	
			9
Various	Pseudo epitheliomatous hyperplasia of the retinal *pigment epithelium*	4	
	Detachment of the retina	2	
			6
			45

shown in Table I The numbers refer to patients The number of eyes examined amounts to 50 as two children were bilaterally enucleated and both eyes were obtained post mortem in three cases The reason for persistent hyperplastic primary vitreous (PHV) *not being represented is twofold first* all the PHV cases within the 25 year period have been examined and published separately (Jensen 1968) and secondly none of these cases was mistaken for a tumour The latter also holds good for our cases of retrolental fibroplasia

We have chosen to group the cases of Coats s disease and suspected Coats s disease as vascular lesions although a vascular malformation probably underlies this exudative retinitis

The cases of septic endophthalmitis were observed in conjunction with severe infectious diseases (meningitis pneumonia) In the two cases of parasitic inflammation serial sections in one case revealed a toxocara like organism in

the retina while the other was suspected of being parasitic because of an abundant eosinophilic infiltration of the retina

All the eyeballs had a normal size apart from nine six of which were microphthalmic (all belonging to the group of malformations) and two buphthalmic (Coats s disease 1 septic endophthalmitis 1) One eye with endophthalmitis was phthisical Cataract was found in a little more than one third with an even distribution over the groups Secondary retinal detachment was seen in a little more than half the cases also within all the groups

Dysplastic changes of the retina as a secondary phenomenon were observed in three eyes with inflammation and one with Coats s disease all in patients under two years of age Calcifications and ossifications appeared in four cases mainly in processes of long standing

Clinical aspects

The distribution of the cases over the 25 year period was uniform at about two cases a year apart from the last two years when no case appeared The Ophthalmic Tumour Clinic at the Ophthalmic Laboratory was established in 1964 The coordinated efforts of this centre and the referring clinical departments have perhaps reduced the number of eyes enucleated based on the vague diagnosis of pseudotumour

In about two thirds of the total material (28 patients) the clinical diagnosis was retinoblastoma and in the remainder (17 patients) a pseudotumour was considered most probable but enucleation was performed since a malignant tumour could not be ruled out Only in two cases was pain the main cause of enucleation

In the first of these groups (clinical diagnosis retinoblastoma) just under half were cases of Coats s disease while in the other group (clinical diagnosis pseudotumour) just under half were cases of inflammation Vice versa in our files there are six cases of retinoblastoma where the clinical diagnosis was a pseudotumour

Sex and age

The sex and age distribution is shown in Fig 1 Males number 26 and females 19 but in the cases of Coats s disease males were double the number of females (11 males 5 females) All the three cases of congenital dysplasia of the retina were girls The highest number of cases was found within the first three years of life as was the case in the retinoblastomas but although 80 per cent of the retinoblastomas were below three years of age at the time of treatment only 53 per cent of the pseudotumours were of that age The youngest patient in the retinoblastoma material was one month and the oldest 9 years among the pseudotumours the corresponding ages were two months and 12 years The

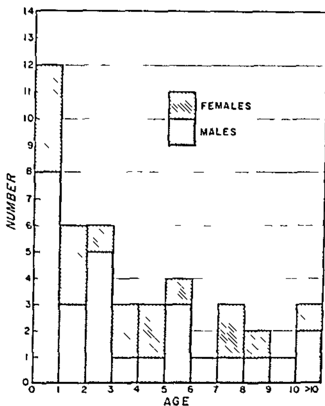


Fig 1
Sex and age incidence in the present series of intraocular pseudotumours in children in Denmark from 1942 to 1966

three patients of an age more than 10 years were two cases of inflammation and one of pseudoepitheliomatous hyperplasia of the retinal pigment epithelium In the present material the three cases of congenital retinal dysplasia were below one year whereas the cases of inflammation were most frequent at the age of two years and of Coats s disease at the age of three More cases of Coats s disease were found at an age of five years than below one year of age

Location

The right eye was affected in 21 cases and the left in 15 and bilateral cases were found in 9 patients The 20 per cent bilateral pseudotumours should be compared with the approximately 30 per cent bilateral retinoblastomas Two children were enucleated bilaterally (tuberous sclerosis and retinal dysplasia) and four with bilateral manifestations had one eye enucleated In only one case (pseudo epitheliomatous hyperplasia of the retinal pigment epithelium) was a

time interval found between the manifestation in right and left eyes Both eyes were obtained post mortem in three cases

No significant overweight of one side was found in any of the groups

Past history

The perinatal abnormalities found were two cases of hemorrhage during pregnancy and two Caesarian sections as well as six cases of prematurity Seven patients were the first child and ten were the last Of these four had Coats s disease and three had other malformations The age of the mothers and any radiotherapy or drug taking during pregnancy could not be established

General diseases were known in 17 cases (40 per cent) These were mainly infectious diseases of childhood It is worth pointing out that of these 17 cases ten had inflammatory ocular processes and in nine of these an infectious disease had preceded the ocular process In addition to toxoplasmosis and tuberculosis (Table I) pneumonia and/or meningitis were the main preceding diseases

The case of ocular tuberous sclerosis had of course a cerebral affection but otherwise no general disease could be related to the ocular change in the remaining cases Traumata in particular could not be elucidated in the two cases where only a detachment of the retina was found Four cases of inflammatory ocular pseudotumour showed defects such as meningocele microcephali small skeletal abnormalities etc One had Down s syndrome General pathological changes seem more frequent in the pseudotumour group than in the retinoblastoma group where only about 10 per cent had or had had general diseases It must of course be borne in mind that the patients with pseudotumours generally belong to a higher age group and consequently have a greater chance of contracting a general disease

Symptoms

In Table II the initial signs and symptoms are listed An attempt has been made in every ca e to discover which symptom had been the first and in most cases this symptom was the abnormality which made the parents seek medical advice

Compared with the retinoblastoma material the two first signs and symptoms (amaurotic cat s eye and squint) have the same order of frequency and are thus of no help in the differential diagnosis but the symptoms of inflamed eyeball and small eye were in no case observed as initial signs and symptoms in the retinoblastoma material It is our experience that microphthalmic eyeballs hardly ever harbour a retinoblastoma The signs and symptoms are spread over all histological groups of pseudotumour but naturally the inflammatory intraocular processes have a tendency to manifest themselves clinically

Table II
Initial signs and symptoms

	Number
Amaurotic cat's eye	10
Squint	7
Inflamed eyeball	6
Impaired vision	6
Small eye*	4
Anomalous pupil	1
Incidental discovery	2
Other symptoms	6
Unknown	3
	45

as red eye* The "other symptoms group comprises photophobia conjunctival discharge etc

Objective findings

As well as anomalous size of the eyeball as mentioned above all kinds of squint and combined forms of squint often irregular positions may be seen and in our material and experience more frequently than among retinoblastoma patients

The anterior segment showed changes much more frequently than in the retinoblastoma material (58 per cent to 19 per cent) These changes were oedema of the cornea in about 20 per cent (associated with glaucoma) and iridocyclitis and its sequelae were found in about a third of the cases These inflammatory changes were most often seen in eyes with an inflammatory process but also in a third of the cases with Coats s disease

Regarding the main process in the vitreal cavity it was described as a retrolental mass of tissue in about one third of the cases and as a more deline ated fundal process in a further third whereas more diffuse descriptions were given in the remaining cases Where the clinical diagnosis was retinoblastoma white retrolental masses were usual but it was not possible to correlate a specific description to a certain histological group In only a few cases of Coats s disease were hemorrhages and crystals described

Radiographically demonstrated calcium is of no use in the differential diagnosis since it is seen in both retinoblastomas and pseudotumours Trans

illumination had been carried out in 25 per cent of the cases and a shadow more or less intense, was found in about half of these In about three quarters *of the retinoblastoma* material a shadow was found but often weak This method of examination appears to be without value in the diagnosis of both groups In our opinion, more modern diagnostic methods such as ultrasonography and fluorescein angiography will be of diagnostic help only in a few special cases

Discussion

The concept pseudoglioma was introduced by Treacher Collins (1893) as a contrast to the true glioma the term then used for retinoblastoma Our nomenclature has been explained in the introduction Disregarding terminology the main problem has always been and still is the differential diagnosis between this varied group of intraocular pathological lesions and the retinoblastoma the malignant ocular tumour of childhood

Pseudotumours are also quantitatively not a negligible problem since between 13 and 15 per cent of the Danish children enucleated in the 25 year *period* concerned had an intraocular pseudotumour whereas *double the number* (27 per cent) had retinoblastoma

After the Second World War a renewed interest in intraocular pseudotumours of children was aroused in connection with the increasing numbers of retrolental fibroplasia and some – but only a few – clinico pathological works have been published up to the present day (Babel 1966 Duke 1958 Hamburg 1963 Heydenreich 1959 Howard & Ellsworth 1965 Kogan & Boniuk 1962 Naumann 1968 O Day 1954 Sanders 1950 Stokes 1953 Wetzel 1941 Zeeman 1931)

In our material the most frequent lesion was Coats s disease, as was also found in several previous materials (Babel 1966 Badtke 1961 Coats 1907 Duke 1958 Hamburg 1963 Lamb 1938 Leber 1916 Manschot & de Bruijn 1967 Morales 1965 Naumann 1968 O Day 1954 Sanders 1950 Stokes 1953)

Coats s original observation that this lesion is mainly unilateral is most frequent in boys and occurs mainly in otherwise healthy individuals can also be confirmed by us In the later stages of this lesion with amaurosis and amaurotic cat s eye or leucocoria (Reese & Blodi 1950) it very much imitates a retinoblastoma and in the group of the present material where the clinical diagnosis was a retinoblastoma half the cases proved to be a Coats s disease

The average age of the patients is however *higher than that of the patients* with retinoblastoma We found it most frequent in the third year of life and more frequent in the fifth than in the first year of life An average age of *eight years* however, has been reported (Morales 1965) as *well* as an average age nearly double that of the average age of retinoblastoma patients (Stokes 1953)

Regarding the next group of frequency the inflammatory ocular pseudo tumours the clinician is much better situated when making a diagnosis Nine patients in our group of 14 such cases had a preceding infectious disease this figure based on anamnestic information must be regarded as a minimum figure Further an inflamed eyeball and recent or old changes in the anterior chamber are also indicative of this lesion

However one third of our cases of Coats s disease had changes of the anterior segment as well But in the differential diagnosis against retinoblastoma *these inflammatory signs in the anterior segment are valuable*

The preceding infectious diseases of the inflammatory pseudotumour were various Most frequent were pneumonia meningitis and toxoplasmosis and chronic infections such as tuberculosis and lues can at present be ignored *in* our country The one case of tuberculous choroiditis dates from 1942

Regarding the malformations the size of the eyeball may be of especial diagnostic value Six of the nine eyeballs with malformations were microphthalmic. In our files we have no microphthalmic eye harbouring a retinoblastoma Although no colobomatous changes were found in our scant material such an observation would support the diagnosis of a benign intraocular lesion Malformations *of the chamber angles and other organs especially of the central nervous* system have the same importance This holds true especially of the phakomatoses but judged from our material general malformations have less use when assessing the character of the pseudotumour since four cases of inflammatory ocular pseudotumour showed various general defects Information on malformations in the family ocular and/or general may be of some use

Several groupings of pseudotumours have been tried more or less comprehensively based on clinical or histopathological characteristics We prefer a histopathological main grouping of four as shown in Table I It must be pointed out that this is not a strict grouping Pseudo epitheliomatous hyperplasia of the retinal pigment epithelium may be secondary to another lesion for instance a small vascular anomaly A case diagnosed as Reese s dysplasia this familiar congenital malformation probably being caused by a genetic defect *may be a retinal dysplasia secondary* to another noxe perhaps a parasite which in the case concerned has not been demonstrated or suspected In our material most of the known diseases causing a pseudotumour are represented except PHV and *retrolental fibroplasia* and some few others But as stated previously no case of PHV or fibroplasia in our files was suspected of being

a retinoblastoma. The reason for this may be that characteristic features for example elongated ciliary processes in the first case and a history of prematurity and oxygen exposition in the second case have left the clinician with little doubt as to the correct diagnosis

Conclusion

Based on the present study of pseudotumours compared with our previous material of retinoblastomas we are able to point out some diagnostic features indicative of pseudotumour and some indicative of retinoblastoma

A. Indicative of pseudotumour are

A high age of childhood a rather long past history, preceding infectious diseases significant preceding trauma animal contacts general malformations prematurity oxygen exposition and as objective findings unilateral affection anomalous size of the eyeball especially microphthalmus accompanying ocular malformations inflammatory signs in the anterior chamber signs of recent and/or old hemorrhage and present signs of general disease (radiographic changes in the lungs positive serological tests eosinophilia of the blood etc)

B. Indicative of retinoblastoma are

Factors opposite to A Especially noticeable is a family history of retinoblastoma eventual enucleation of unknown cause normal size of the eyeball normal anterior chamber and as a special and valuable sign when possible to detect the presence of multiple foci or implantations in the retina and/or in the anterior chamber In addition excretion in the urine of vanilmandelic acid and/or homovanillic acid may be a valuable sign

It is the sum of all these parameters and the experience of the clinician which may determine the correct diagnosis but it will always be wise to enucleate a useless eye since even the most experienced can be misled

Every ophthalmological department and ophthalmic pathology laboratory must strive to make as exact a diagnosis as possible preferably a pathogenetical one and avoid the omnibus item pseudotumour

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Requests for reprints should be addressed to O A Jensen Ophthalmic Pathology Laboratory Tagensvej 18 DK 2200 Copenhagen N Denmark

From Oslo University Eye Department
(Head: Professor dr. med. Thore L. Thomassen)
and Neurosurgical Department
(Head: Professor dr. med. Tormod Hauge)
Rikshospitalet, Oslo, Norway

DYNAMIC TONOMETRY IN CAROTID OCCLUSIVE DISEASE

BY

IVAR HØRVEN, HELGE NORNES, PER SYPDALEN & ASBJØRN M. TONJUM

Carotid occlusive disease may *change intraocular* pressure in three ways as shown in Fig. 1. First, the intraocular pressure may be moderately decreased on the symptomatic side (Bynke 1960, *Nornes et al. 1971b*). Second, the corneal indentation pulse (C.I.P.) *amplitudes* may be reduced to 70-80 per *cent* of the normal values (Nornes et al. 1971a, Nornes et al. 1971b). Third, an increase may be present in the relative crest time of the C.I.P. (Hørven & Nornes 1971).

These three parameters have been studied in detail in groups of patients with carotid occlusive disease and will be briefly commented.

Methods

Dynamic tonometry *is performed* under topical anesthesia in the supine position just like an ordinary Schiøtz tonometry. The dynamic tonometer (Hørven 1968) is an improved electronic Schiøtz tonometer supplied with a zero suppression unit. The output is 1 mV per 1 μ plunger deflection, which permits accurate recording of the corneal indentation pulse (C.I.P.) amplitudes at all tension levels.

Address for reprints: Ivar Hørven, Eye Department, Rikshospitalet, Oslo, Norway.
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These three parameters have been studied in detail in groups of patients with carotid occlusive disease and will be briefly commented

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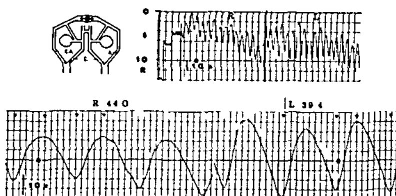


Fig 1

Dynamic tonometry in right sided carotid occlusive disease (Right I C A full occlusion Right E C A marked stenosis Left I C A minor negligible stenosis) Pathological results are demonstrated in three parameters Intraocular pressure (decrease) corneal *indentation pulse amplitudes (decrease) and relative crest time (increase)*

Various sensitivity settings and paper speeds are used during the examinations First the eye tension is recorded with the 5 5 g plunger weight (right eye – left eye) with a sensitivity setting of 20 mV (= 20 μ) per paper division and a paper speed of 1 mm per second The eye tension in scale reading Schiotz (R) may be converted into mm Hg intraocular pressure (P_o) by the use of Friedenwald s 1955 converting table Thereafter the C I P amplitudes are recorded in

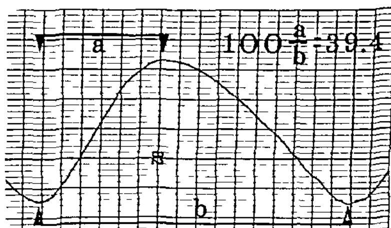


Fig 2

Method of relative crest time determination a = time in seconds from base to summit of the pulse curve b = time in seconds of one heart cycle $\frac{a \cdot 100}{b}$ = relative crest time in per cent

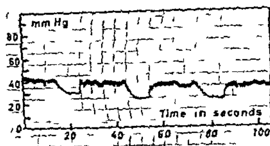


Fig 3

Decrease in intraocular pressure caused by digital compression of the ipsilateral common carotid artery (Ytteborg 1960)

detail with a sensitivity setting of 2 mV (= 2 μ) per paper division and a paper speed of 5 mm per second Finally the relative crest time studies (Horven & Nornes 1971) or carotid compression tonographic tests (Horven et al 1971) are performed with a suitable sensitivity *setting and paper speed* By relative crest time of the C I P amplitudes is understood the time from base to summit of the pulse curve calculated in per cent of one heart cycle as shown in Fig 2

Results and Comment

Intraocular pressure

An abrupt full *occlusion as produced in Fig 3 by digital* compression of the common carotid artery (Ytteborg 1960) or initiated by clamping of the internal carotid artery (I C A) (Nornes et al 1971a) is followed by a prompt reduction of intraocular pressure to about 50 per cent of the initial value After a short while collateral blood supply to the eye will develop with an increase in intraocular *pressure to subnormal or normal* levels Bynke (1966) found equal intraocular pressure on both eyes in 8 and a 1 3 mm Hg decrease on the symptomatic side in 9 of his 17 patients with unilateral carotid occlusive disease Our group of 27 patients 15 unilateral and 12 bilateral demonstrated an average intraocular pressure of 14 0 mm Hg on the symptomatic side compared with 15 2 mm Hg on the *other side (Nornes et al 1971b) As judged by the* statistical method of paired comparison this difference was found significant at the 1 per cent level

If therefore routine tonometry reveals a repeated difference of 1 2 scale reading Schiotz carotid occlusive disease is one of the possible explanations that should be considered This hypotension is apparently an expression of the reduced blood flow through the ciliary body (Hoyt 1959)

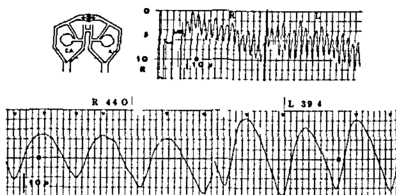


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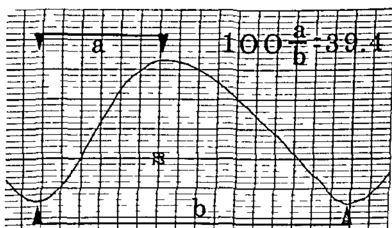


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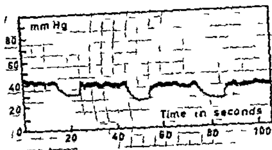


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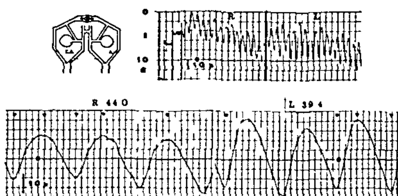


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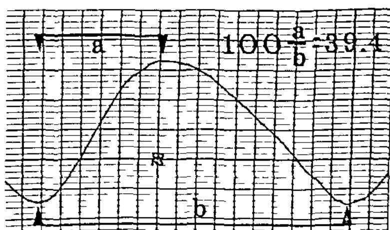


Fig 2

Method of relative crest time determination a = time in seconds from base to summit of the pulse curve b = time in seconds of one heart cycle $\frac{a \cdot 100}{b}$ = relative crest time in per cent

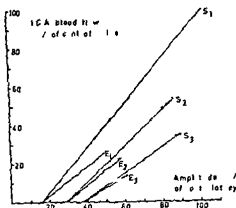


Fig 5

Correlation between internal carotid artery blood flow and corneal indentation pulse amplitudes during three graded occlusions of internal carotid artery The increase in corneal indentation pulse amplitudes at zero flow at subsequent occlusions demonstrates the development of collateral blood supply to the eye Average results of 10 patients S_1 = start E_1 = end of first days graded occlusion. Second occlusion (S_2-E_2) and third occlusion (S_3 E_3) were performed after an average of 2 8 days and 6 5 days respectively

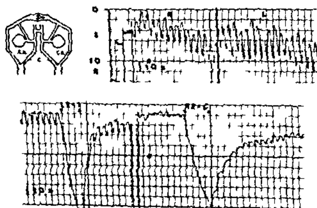


Fig 6

Carot d compression tonographic tests on patient demonstrated in Fig 1 The right eye is supplied with blood from the left carotid artery system as a marked reduction in both intraocular pressure and corneal indentation pulse amplitudes is demonstrated on the right eye by digital compression of the left common carotid artery (RE C)

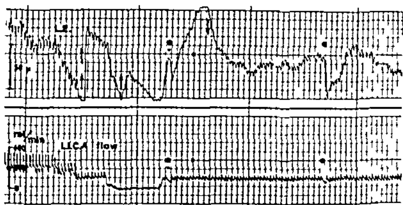


Fig 4

Simultaneous recording of corneal indentation pulse amplitudes (above) and internal carotid artery blood flow (below) during graded occlusion of internal carotid artery with the Selverstone clamp Each arrow zero suppression (or reset) of 50 mV = 50 microns of plunger movement i e one scale reading Schiotz e = extrasystole

Corneal Indentation pulse amplitudes

The relation between C I P amplitudes and blood flow of the ipsilateral I C A has been studied in detail during graded occlusion of I C A in 10 patients with intracranial aneurysms (Nornes et al 1971a) A Selverstone clamp was used and an electromagnetic flowmeter was placed around the I C A just cranially to the clamp The therapeutic goal was through graded occlusions to establish a final I C A blood flow of 15 per cent of normal value

During graded occlusion a simultaneous recording was performed of C I P amplitudes and I C A blood flow as shown in Fig 4 A very close correlation was noted When a reduction in flow was obtained a corresponding decrease in C I P amplitudes was seen The average values of the 10 patients are shown in Fig 5 A decrease in C I P amplitudes to 16 per cent of normal value was initiated by first days clamping to zero I C A flow The Selverstone clamp was reopened to 25 per cent I C A flow with a corresponding increase in C I P amplitudes The next morning a 50 per cent I C A flow value was recorded while the C I P amplitudes measured 85 per cent of the normal value This observation points towards the development of collateral blood supply to the eye Clamping to zero I C A flow gave this second day C I P amplitudes of 29 per cent while clamping to zero I C A flow six days later gave C I P amplitudes of 38 per cent of normal values Accordingly the eye has an enormous capacity for collateral blood supply which needs from only hours to a few days to develop When the I C A blood flow ceases because of obstruction the eye will be supplied from the ipsilateral external carotid artery from the contralateral carotid arteries or in some cases even from the vertebral arteries (Horven et al 1971)

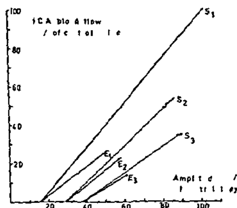


Fig 5

Correlation between internal carotid artery blood flow and corneal indentation pulse amplitudes during three graded occlusions of internal carotid artery. The increase in corneal indentation pulse amplitudes at zero flow at subsequent occlusions demonstrates the development of collateral blood supply to the eye. Average results of 10 patients. S_1 = start E_1 = end of first days graded occlusion. Second occlusion (S_2-E_2) and third occlusion (S_3 E_3) were performed after an average of 2 8 days and 6 5 days respectively

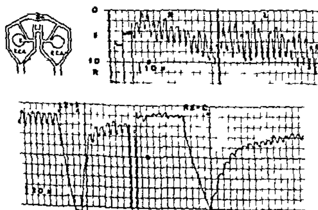


Fig 6

Carotid compression tonographic tests on patient demonstrated in Fig 1. The right eye is supplied with blood from the left carotid artery system as a marked reduction in both intraocular pressure and corneal indentation pulse amplitudes is demonstrated on the right eye by digital compression of the left common carotid artery (RE C)

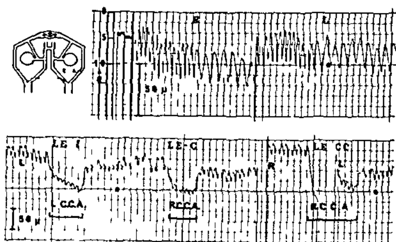


Fig 7

Dynamic tonometry results and carotid compression tonographic tests responses following graded occlusion of left internal carotid artery The left eye is supported partly by the ipsilateral external carotid artery and partly by the contralateral carotid arteries LL I tonometry left eye during left common carotid artery (L C C A) compression LE C tonometry left eye during right common carotid artery (R C C A) compression. LE CC tonometry right eye during right common carotid artery (R C C A) compression When a positive response is observed the tonometer is moved to the left eye while the compression of R C C A is continued

This will be elucidated in a couple of figures Fig 6 demonstrates the results of digital compression of the common carotid artery in the patient also presented in Fig 1 By digital compression on the left side (LE I) a normal response with marked reduction of intraocular pressure was observed in the left eye No response was demonstrated in the right eye when the right side was compressed A marked reduction of intraocular pressure was however initiated in the right eye by digital compression of the left common carotid artery (RL C) This demonstrates clearly that the right eye of this patient was supplied with blood from the left carotid artery system Fig 7 demonstrates the situation 9 months following clamping of the left I C A in a female aged 32 At this time a close to full occlusion of the left I C A was found with only traces of contrast passing the clamped segment of the artery by angiography The C I P amplitudes of the left eye were reduced but not totally neutralized by digital compression of either right or left common carotid artery Accordingly the left eye was supplied with blood partly from the left external carotid artery through anastomoses with the left ophthalmic artery and partly from the right carotid artery system In this patient the collateral blood supply of the left eye was so extensive that both intraocular pressure and C I P amplitudes yielded close to normal values Recording of C I P amplitudes as the only parameter of study is there

fore not sufficient to establish the diagnosis in all cases of carotid occlusive disease the carotid compression tonographic tests may offer valuable additional information Digital compression of the common carotid artery should be performed with care as the procedure is not without danger Hemiplegia (Askey 1946) and death (Nelson & Mahru 1963) have been reported

Pathological results were obtained in 100 per cent of our 15 patients with unilateral spontaneous carotid occlusions by the use of dynamic tonometry and carotid compression tonographic tests (Nornes et al 1971b) Of the 12 bilateral cases pathological results were obtained in 10 i e in 83 per cent

Relative crest time

Table I summarizes the results obtained in various groups of patients with disorders affecting the ocular blood supply The study of relative crest time is most important in the evaluation of carotid cavernous sinus fistula and giant cell arteritis with ocular involvement (Hørven & Nornes 1971) As shown in Fig 1 the relative crest time is moderately increased on the symptomatic side by carotid occlusive disease Table I gives a normal relative crest time average of 41 5 per cent σ = 2 336 indicating that 99 per cent of the normal population should yield a relative crest time of 41 5 per cent ± 2 58 × 2 336 i e between 35 5 and 47 5 per cent The 17 patients with carotid obstructions (7 unilateral and 10 bilateral) gave a relative crest time average of 45 4 per cent on the symptomatic side Four of these 17 patients showed relative crest time values above 47 5 per cent that is above the upper normal limit This is most important as it suggests that evaluation of relative crest time may give pathological results in some cases by the study of only one eye provided that this eye is on the symptomatic side

Table I

Average value of relative crest time in various groups of patients

Groups of patients	No of eyes	Relative crest time			Significance level
		x̄	σ	t value*	
Normal	0	41.5	2 336		
Carotid obstruction	17	45 4	3 517	3 893	P < 0 001
Giant cell arteritis	13	48 6	2 8 8	534	P < 0 001
Carotid cavernous sinus fistula	4	54 8	2 995	4 775	P < 0 001

* Student t tests

Summary

This clinical study was performed by use of dynamic tonometry an easy and accurate method for screening diagnosis of alterations in ocular blood supply A decrease in intraocular pressure (Schiotz) and corneal indentation pulse amplitudes and an increase in relative crest time of the corneal indentation pulse were demonstrated on the symptomatic side in groups of patients with carotid occlusive disease

Acknowledgement

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From the Eye Clinic University of Helsinki Finland
(Head Prof Salme Vannas M D)

MYELINATED NERVES OF THE PIG IRIS

BY

MATTI SAARI

The rich innervation of the iris was already known in the latter part of the 19th century (Arnold 1863 Pause 1877 Meyer 1879 Hosch 1891 Andogsky 1897) In recent years the new methods now available have revived interest in iris innervation It was while developing methods for the study of iris capillaries that the problem of this innervation was encountered (Saari 1970 1971a 1971b) The purpose of the present paper is to describe the myelinated innervation of the pig iris in greater detail The autonomic innervation of the pig iris (Werner 1962 Lukaš 1964 Niemi & Tarkkanen 1964 Lukáš & Čech 1965 Lukaš & Čech 1966) is not dealt with

Material and Methods

A. Microscopic examination

Fresh pig eyes from an abattoir were used

The flat preparation method (Saari 1970) was used to examine 20 irises with PAS hematoxylin staining after potassium permanganate and oxalic acid bleaching

3 irises were examined after trypsin digestion and potassium permanganate bleaching (Saari 1971a) with PAS hematoxylin Alcian blue (ICI) or Alcian blue (ICI) PAS hematoxylin staining

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After a 20 hour trypsin digestion and potassium permanganate bleaching (Saari 1971a), 10 irises were examined with Sudan black staining and 16 irises with osmic acid staining

Six irises after a 20 hour trypsin digestion and potassium permanganate bleaching were stained with PAS hematoxylin and covered with a glass plate fastened with glycerin jelly The preparation was photographed The cover glass was removed with the aid of warm water the preparation rinsed with distilled water bleached for an hour in 0 25 per cent potassium permanganate solution and rinsed in distilled water It was then kept for 6 min in 5 per cent oxalic acid solution and again rinsed in distilled water By this time all colour had been removed from the preparation It was now stained with Sudan black and re photographed The photographs were compared

Neoprene latex coloured red was injected into the long posterior ciliary artery, and Neoprene latex coloured blue into the vortex vein of 15 pig eyes The irises were examined by the injection digest bleaching method (Saari 1971b)

Four pig eyes were fixed in 10 per cent neutral formalin and serial paraffin sections were cut at 5 to 8 microns The sections were treated with Nassar s silver staining Bodian s (1936) method for nerve fibres and nerve endings or with a combined staining for fibres and cells of nervous system (Kluver & Barrera 1953)

B Electron microscopic examination

Fifteen pig irises were examined Immediately the pig had been killed in the abattoir the eye was enucleated the iris was dissected free and cut into small pieces which were fixed in 3 per cent glutaraldehyde (Fluka AG Buchs) at +4° C for 2 hours (Sabatini Bensch & Barrnett 1963) They were rinsed with phosphate buffer Postfixation was done with 1 per cent Osmium tetroxide (Merck) buffered at pH 7 2 with phosphate buffer at +4° C for 90 min For dehydration the pieces were kept 5 min in 50 per cent ethyl alcohol 10 min in 70 per cent ethyl alcohol 30 min in 94 per cent ethyl alcohol and 60 min in absolute ethyl alcohol The alcohol was removed with propylene oxide (Fluka AG Buchs) for 30 min and the preparation was embedded in Epon 812 (Luft 1961) Thick and thin sections were cut with ultramicrotome (Sorvall Porter Blum MT 1) fitted with glass knives Thick sections for light microscopy were mounted on glass slides and stained with toluidin blue Thin sections for electron microscopy were stained with lead citrate (Reynolds 1963) or double stained with uranyl acetate (Watson 1958) and lead citrate Electron micrographs were taken with a UEMB 100B electron microscope at original magnifications of 2000 to 90 000 and enlarged as desired

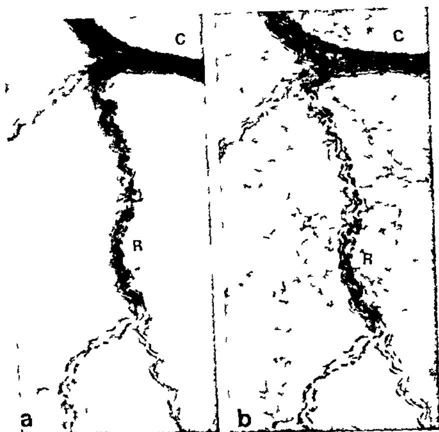


Fig 1a b

a Flat preparation of pig iris treated with 90 hour digestion bleaching and PAS hematoxylin staining The circular nerve bundle (C) and radial nerve branches (R) of the ciliary part are visible × 80

b The same preparation after a second bleaching and Sudan black staining The course of myelinated nerve fibres shows off in the same way as with PAS hematoxylin staining × 80

Results

Staining of myelinated nerves in flat preparations

By PAS hematoxylin staining after potassium permanganate bleaching the myelinated nerves showed up dark purple in colour Rich myelinated innervation was observed in the pig iris

After trypsin digestion and potassium permanganate bleaching the myelinated nerves showed up well staining dark purple with PAS hematoxylin and black with Sudan black With osmic acid staining the myelinated nerves stained

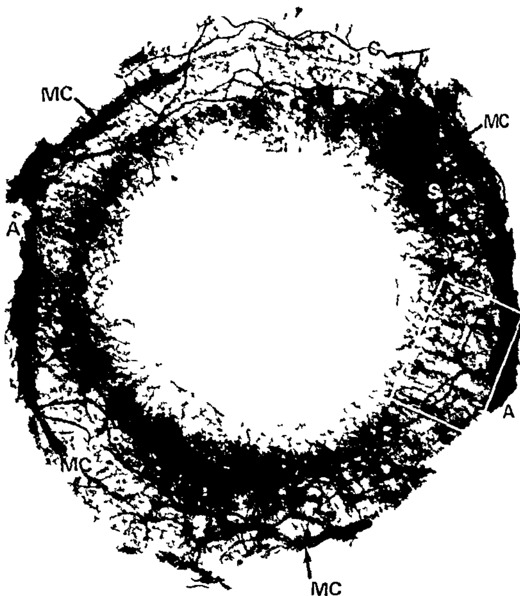


Fig 2a

Fig 2a b

Flat preparation of pig iris treated with 20 hour digestion and bleaching PAS hematoxylin

a The long posterior ciliary artery and nerve enter the iris (A) The major arterial circle of the iris (MC) the circular (C) and radial (R) nerve bundle of the ciliary part the circular nerve bundle at the borderline of the ciliary and pupillary parts (B) are visible Myelinated nerves show a nearly stellate intersection (S) × 9

b Detail from Fig 2a Radial vessels (V) Myelinated nerve branches running towards the pupillary part (P) × 32

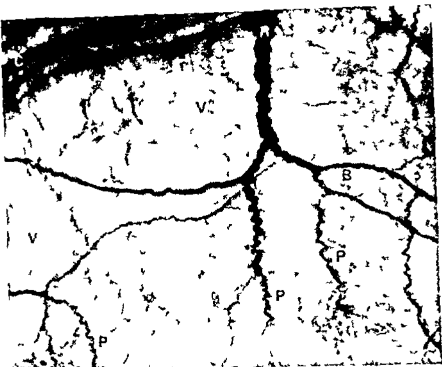


Fig °b

dark but did not show up so well as with PAS hematoxylin or Sudan black *staining for the background also stained yellow or brown*

After trypsin digestion and potassium permanganate bleaching the flat preparation (Fig 1a) of pig iris stained with PAS hematoxylin showed the course of the myelinated nerve fibres in the same way as the same preparation (Fig 1b) after a second potassium permanganate bleaching and Sudan black staining

The course of myelinated nerves in pig iris

In the pig s eye the long posterior ciliary artery and nerve enter the iris on the nasal and temporal sides respectively (Fig 2a) Before entering the iris the long posterior ciliary nerve sends a plexus of myelinated nerves on each side of the ciliary body The long posterior ciliary nerve sends the main branches to the iris where they have an upward and downward course on the nasal and temporal side Passing circularly in the ciliary part of the iris they send myelinated branches to the pupillary part.

The circular nerve bundles of the ciliary part of the iris are strongly developed and anastomose with the plexus of the ciliary body In the ciliary part of

the iris the circular nerve bundles run an irregular course They may run in an arch on the ciliary body side and return to the ciliary part of the iris The plexus of the ciliary part is strongest near the long posterior ciliary nerve and in its circular course it sends either gently curving or radial corkscrew shaped branches towards the pupillary part (Fig 2a) At the point where the long posterior ciliary nerve enters the iris strongly developed radial nerve bundles are often directed towards the pupillary part (Fig 2b) The ciliary part of the iris also shows individual myelinated nerve fibres The circular nerve bundles of the ciliary part entering from the nasal and temporal sides of the iris also anastomose in the upper and lower parts of the iris (Fig 2a)

The fibre bundles running from the ciliary to the pupillary part form a new circular plexus at the borderline between them From this plexus branches continue to the pupillary part or they may re-curve towards the ciliary part (Figs 2a and 2b)

The nerve bundles directed towards the pupillary part are divided into two branches each passing towards the pupillary margin and re dividing (Fig 2b) On division and intersection the myelinated nerves form in the pupillary part rhomb shaped configurations at first with a large mesh but closer to the pupillary margin with a small mesh (Fig 3) Division reduces the number of nerve fibres in each branch to a few and at last to one Hence the single myelinated nerve fibres are most numerous in the pupillary part

Relationship to blood vessels

The myelinated nerves do not accompany the blood vessels in the pig iris In the injection digest bleaching preparations the major arterial circle venous trunks and deep capillaries were seen at the back of the myelinated nerves The radial arteries were in front or at the back of the myelinated nerves the superficial capillaries in front of them Some venules running from the ciliary part of the iris to the ciliary body were seen anterior to the myelinated nerve bundles In the pupillary part myelinated nerves were mostly in front of the blood vessels

Some myelinated nerve fibres could be observed deeper in the stroma A number of them in the posterior part of the stroma had a radial course in corkscrew form from the cilliary body plexus to the pupillary part without anastomosing with the circular nerve bundles of the ciliary part

Relationship to collagen fibres of the stroma

The myelinated nerves follow the course of the collagen fibres in the stroma of the iris The collagen fibres in the ciliary part run a more circular course but on approaching the pupillary margin they assume an increasingly radial course



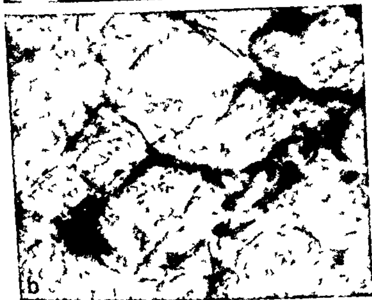


Fig 3a b

Flat preparation of pig iris treated with 13 hour digestion and bleaching PAS hematoxylin × 00 The myelinated nerves in the pupillary part form rhombs with a relatively large mesh (a) which becomes smaller as it approaches the pupillary margin (b)

the iris, the circular nerve bundles run an irregular course They may run in an arch on the ciliary body side and return to the ciliary part of the iris The plexus of the ciliary part is strongest near the long posterior ciliary nerve and in its circular course it sends either gently curving or radial corkscrew shaped branches towards the pupillary part (Fig 2a) At the point where the long posterior ciliary nerve enters the iris strongly developed radial nerve bundles are *often directed towards the pupillary part (Fig 2b) The ciliary part of the iris* also shows individual myelinated nerve fibres The circular nerve bundles of the ciliary part, entering from the nasal and temporal sides of the iris also anastomose in the upper and lower parts of the iris (Fig 2a)

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Relationship to collagen fibres of the stroma

The myelinated nerves follow the course of the collagen fibres in the stroma of *the iris* The collagen fibres in the ciliary part run a more circular course but on approaching the pupillary margin they assume an increasingly radial course



Fig ɔa b

a Light micrograph from the c liary part of the pig iris fixed in glutaraldehyde and osmium The myel n sheaths of nerve fibres appear as blackened rings in the nerve bundles (arrow) Toluidin blue × 450

b Electron m c ograph of a thin section from the same area of the specimen. 18 mye linated nerve fibres are seen in the nerve bundle this is surrounded by a perineurial sheath (PN) Uranyl acetate followed by lead citrate × 4190

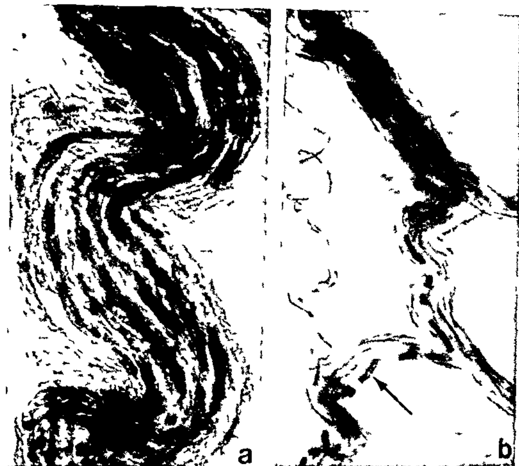


Fig 4a b

Flat preparation of pig iris treated with 20 hour digestion and bleaching PAS hema toxylin

a The radial nerve bundle of the ciliary part close to the pupillary part runs in cork screw form parallel with the course of the collagen fibres The myelinated nerve fibres show an almost parallel mutual arrangement × 900

b *The radially* running nerve bundle is thinner after its division The nerve bundle contains thicker (arrow) and thinner myelinated nerve fibres × 250

The myelinated nerves in the ciliary part run a circular course and on branch ing off they curve gently following the course of collagen fibres towards the pupillary part Or accompanying in turn the collagen fibres arriving from opposite directions they may assume a radial course in corkscrew form

Thickness of nerve bundles and the course of an individual nerve fibre in the nerve bundle

The circular myelinated nerve bundles in the ciliary part are relatively thick After branching off radially they become narrower Some of the radial nerve



Fig 6

Myelinated (MF) and non myelinated (NMF) nerve fibres and collagen fibrils (CF) in the stroma of pig iris Lead citrate × 10180

sists of a nucleus cytoplasm with mitochondria the Schwann cell surface and a thin basement membrane The Schwann cell surface is connected by a double edged membrane (mesaxon) to the myelin sheath which surrounds the axon Axoplasm contains mitochondria with the typical internal membranes axofila ments axoplasmic vesicles and neurotubules Axoplasm is surrounded by axo lemma (Fig /a)

Larger magnification (Fig /b) reveals a distinct concentric lamellar periodic structure in the myelin sheath with the major dense lines and less dense bands alternating In the region of compact myelin the thickness of a layer consisting of a major dense line and a less dense band is 124 Å Between two major dense

bundles are also thick (Fig 4a) After division the nerve bundle is thinner (Figs 2b and 4b) On reaching the pupillary edge the nerve bundle contains only a few myelinated nerve fibres which continue to branch until there is only one myelinated nerve fibre (Fig 3b)

The myelinated nerve fibres in a nerve bundle run parallel to one another (Fig 4) At the point of division of the nerve bundle, some nerve fibres continue along one branch and others take the other (Figs 1 and 4b) Some fibres of a myelinated nerve bundle may branch and immediately join another nerve bundle thus changing over from one nerve bundle to another Two nerve bundles may meet in such a manner that a number of fibres in each change over to another nerve with decussation whereas others run without decussation Myelinated nerves divide and intersect in various ways and myelinated nerve fibres change over from one nerve bundle to another thus forming a multiform plexus of myelinated nerves in the pig iris

Myelinated nerve fibres

The individual myelinated nerve fibres in the pig iris are not all of the same thickness Two types of fibres of different thickness were noted in the digested and bleached flat preparations of pig iris (Fig 4b) The thinner myelinated nerve fibres were present all over the iris They varied slightly in thickness but were definitely thinner than the thicker myelinated nerve fibres The latter came from the long posterior ciliary nerve and occurred in the nasal and temporal part of the iris less frequently in the upper and lower part Their circular course in the ciliary part of the iris was usually short and they then followed the radial nerve trunks towards the pupillary part where they stopped just short of the pupillary margin

Myelinated nerves in serial section preparations

The myelinated nerves did not manifest themselves well in the ordinary formalin fixed paraffin sections In the glutaraldehyde and osmium fixed sections stained with toluidin blue they were better visualised Myelinated nerve bundles were *found in the ciliary part of the pig iris* (Fig 5a) The course of the myelinated nerves in the pig iris could not be so well followed in serial sections as in flat preparations

Ultrastructure of myelinated nerves

Electron microscopic examination revealed both myelinated and non myelinated nerves in the stroma of pig iris (Fig 6) Nerve bundles containing several myelinated nerve fibres were seen in the ciliary part (Fig 5b)

The Schwann cell carries only one myelinated axon The Schwann cell con

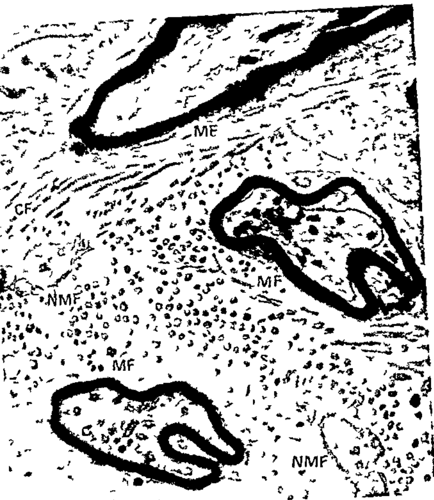


Fig 6

Myelinated (MF) and non myelinated (NMF) nerve fibres and collagen fibrils (CF) in the stroma of pig iris Lead citrate × 10180

sists of a nucleus cytoplasm with mitochondria the Schwann cell surface and a thin basement membrane The Schwann cell surface is connected by a double edged membrane (mesaxon) to the myelin sheath which surrounds the axon Axoplasm contains mitochondria with the typical internal membranes axofilaments axoplasmic vesicles and neurotubules Axoplasm is surrounded by axolemma (Fig 7a)

Larger magnification (Fig 7b) reveals a distinct concentric lamellar periodic structure in the myelin sheath with the major dense lines and less dense bands alternating In the region of compact myelin the thickness of a layer consisting of a major dense line and a less dense band is 124 Å Between two major dense



Fig. 7a

lines there is an intraperiod or intermediate line which is more delicate than the major dense line The inner Schwann cell plasma membrane is inside the myelin sheath and an axon plasma membrane is inside the inner Schwann cell plasma membrane Together they form the axon Schwann membrane or axolemma



Fig 7b

Fig 7a b

a. The myelinated axon is surrounded by the Schwann cell in which can be discerned nucleus (Scn) cytoplasm with mitochondria (M) Schwann cell surface and a thin basement membrane A double edged membrane (arrow) connects the Schwann cell surface to the myelin sheath (My) which surrounds the axon Axoplasm contains mito chondria (AxM) axofilaments neurotubules and axoplasmic vesicles (AxV) Lead ci trate × 31000

b Detail from F g a The lamellar structure of the myel n sheath with major dense lines and less dense bands alternating The intermediate line (arrow) is also visible The inner Schwann cell plasma membrane (IPM) and axon plasma membrane (APM) are discernernible in the axolemma Axofilaments (AxF) neurotubules (NT) × 159 000

Discussion

The innervation of the iris studied by earlier ordinary methods has been grossly described as follows Nerve trunks in the ciliary part of the iris run circularly and radially oriented nerves branch off from them towards the pupillary margin (Arnold 1863 Pause 1877 Meyer 1879 Hosch 1891 Andogsky 1897 Beatie & Stilwell 1961, Castro Correia 1967) In the present study when flat preparation techniques were used the myelinated nerve bundles from the long posterior ciliary nerve to the iris were found to run upward and downward on the nasal and temporal sides in the ciliary part of the iris In their circular course they sent myelinated branches to the pupillary part The ciliary part was also found to contain single myelinated nerve fibres although their existence had been denied by Pause

The myelinated nerves mostly run on the surface of the iris (Iwanoff 1874) above the large vessels (Pause Meyer), with capillaries above them (Agababow 1912) In the present work the major arterial circle of the iris venous trunks deep capillaries and some of the radial arteries in the ciliary part were found to be at the back of the myelinated nerve bundles whereas other radial arteries some venules running from the ciliary part of the iris to the ciliary body and the superficial capillaries were above them A few myelinated nerve fibres were seen at a depth in the stroma In the pupillary part, most myelinated nerves were on top of the vessels

The opinion that iridic nerves do not follow the course of the blood vessels was advanced early (Arnold Pause) The vasomotor nerves of the iris were a later finding (Meyer Hosch Andogsky Kirpitschowa Leontowitsch 1911 Agababow) They accompanied and surrounded arteries and capillaries By means of formaldehyde induced fluorescence (Eranko 1952 1955 1967) adren ergic nerve fibres can be demonstrated surrounding the iridic vessels as has also been reported for the pig iris (Lukaš & Čech 1966) According to Castro Correia (1967) the thinnest myelinated nerve branches follow the vessels The present work showed however that the myelinated nerves run in the stroma of *pig iris independently without accompanying the blood vessels*

Pause and Meyer noticed that radial nerve fibres in the iris ran a corkscrew like course Schinnert (1936) found that the nerves of the iris formed a rhomboid network and Castro Correia observed a nervous net of diamond shaped mesh

The connective tissue fibres of the iris are regularly arranged In the ciliary part they run a more circular and in the pupillary part a more radial course (H Rohen 1951 J W Rohen 1964) According to an earlier report the blood vessels and pigment cells of the iris are arranged in conformity to the system of connective tissue fibres (H Rohen) In the present work the myelinated nerves in the pig iris also showed an arrangement in conformity to the system of connective tissue fibres

Ernyei (1934) also studied the pig iris and found that the myelin sheaths in the individual nerve bundles of the iris were of equal thickness The present finding was however that the myelinated nerve fibres in pig iris differed in thickness There were both thin and thick nerve fibres The thinner myelinated nerve fibres occurred over the whole area of the iris and could differ slightly in thickness but they were definitely thinner than the thicker myelinated nerve fibres running in the more temporal and nasal areas of the iris from the long posterior ciliary nerve along the radial nerve bundles close to the pupillary margin The same nerve bundle could contain both thick and thin myelinated nerve fibres (Fig 4b)

Tousimis & Fine (1959) on electron microscopic examination of the iris of man and monkey found mitochondria and filaments 100 Å in diameter in the axoplasm of myelinated fibres Electron microscopic examination of the iris of the house cat (Krapp 1962) and albino rabbit (Richardson 1964) revealed myelinated nerve fibres having a separate Schwann sheath Myelinated and non myelinated nerves were noted by electron microscopic examination in the iris of dog (Shively & Epling 1969) In the present work the ultrastructure of the myelinated nerves of the pig iris was described in detail

The present study revealed a spacing of 124 Å of the major dense lines in the area of compact myelin of the myelinated nerves of the pig iris This is of the same order as the myelin period of 120 130 Å observed in the myelinated nerves of the iris angle of man and the rhesus monkey (Chapman & Spelsberg 1963)

Summary

1 The myelinated nerves of the pig iris were studied by flat preparations serial sections and electron microscopic technique

2 The course of the myelinated nerves in the pig iris is described

3 In the ciliary part of the pig iris there are also single myelinated nerve fibres

4 The myelinated nerves of the iris are arranged in conformity to the system of connective tissue fibres

5 In the stroma of the pig iris the myelinated nerves do not follow the course of the blood vessels

6 In digested and bleached flat preparations the myelinated nerve fibres were found to be of two thicknesses The thinner ones occurred all over the iris the thicker mainly in the nasal and temporal parts of the iris

7 The ultrastructure of the myelinated nerves of pig iris is described.

Discussion

The innervation of the iris studied by earlier ordinary methods has been grossly described as follows. Nerve trunks in the ciliary part of the iris run circularly and radially oriented nerves branch off *from them towards the pupillary margin* (Arnold 1863, Pause 1877, Meyer 1879, Hosch 1891, Andogsky 1897, Beatie & Stilwell 1961, Castro Correia 1967). In the present study, when flat preparation techniques were used, the myelinated nerve bundles from the long posterior ciliary nerve to the iris were found to run upward and downward on the nasal and temporal *sides in the ciliary part of the iris. In their circular course they* sent myelinated branches to the pupillary part. The ciliary part was also found to contain single myelinated nerve fibres, although their existence had been denied by Pause.

The myelinated nerves mostly run on the surface of the iris (Iwanoff 1874) above the large vessels (Pause, Meyer) with capillaries above them (Agababow 1912). In the present work, the major arterial circle of the iris, venous trunks, deep capillaries and some of the radial arteries in the ciliary part were found to be at the back of the myelinated nerve bundles, whereas other radial arteries, some venules running from the ciliary part of the iris to the ciliary body and the superficial capillaries were above them. A few myelinated nerve fibres were seen at a depth in the stroma. In the pupillary part, most myelinated nerves were on top of the vessels.

The opinion that iridic nerves do not follow the course of the blood vessels was advanced early (Arnold, Pause). The vasomotor nerves of the iris were a later finding (Meyer, Hosch, Andogsky, Kirpitschowa Leontowitsch 1911, Agababow). They accompanied and surrounded arteries and capillaries. By means of formaldehyde induced fluorescence (Eränkö 1952, 1955, 1967) adrenergic nerve fibres can be demonstrated surrounding the iridic vessels, as has also been reported for the pig iris (Lukas & Čech 1966). According to Castro Correia (1967) the thinnest myelinated nerve branches follow the vessels. The present work showed, however, that the myelinated nerves run in the stroma of pig iris independently, without accompanying the blood vessels.

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A bilaminar structure of the peripheral part of the anterior lens capsule has been established by light microscopy and by electronmicroscopic examinations of lenses with so called senile exfoliation or pseudoexfoliation (Bertelsen Drablos & Flood 1964 Ashton et al 1965) A deep layer sandwiched between the cellular layer and the proper capsule contains bundles of a fibrillar material which has an ultrastructure similar to that found in the deposits of the anterior lens surface and other structures which are in contact with aqueous humour Bertelsen, Drablos & Flood (1964) showed that bundles of fibrillar material seemed to be emerging from pits in the epithelial surface membrane The actual orientation of these bundles was perpendicular to the capsular surface producing a striated appearence of the deep layer when studied in sections In the superficial proper capsule clefts dots and patches were found which by electron microscopic examinations proved to consist partly of granules and partly of fibrils with a structure similar to that of the fibrils found in the deep layer and on the capsule surface This observation led to the theory that the fibrillar substance is synthesized by the epithelial cells of the lens Hence the name fibrillopathia epitheliocapsularis was suggested for this condition

A more recent work (Bertelsen & Ehlers 1969) showed that the distribution of the deep layer was limited to a pre equatorial zone localized just central to the peripheral border of the cell layer and with a maximum width of 1 5 mm The deep layer was present in all the lenses with fibrillopathy but the amount varied greatly It could not be traced in control lenses The deep layer was found to be a rather interrupted structure covering at most 13 epithelial cells This suggested that the deep layer probably had a patchy localisation in the above mentioned zone

Dark Streeten & Jones (1969) have confirmed most of these observations and they have sought to relate these findings to the presence of formed elements in the normal lens capsule These authors also demonstrated fibrillar protein in aging lens capsules without fibrillopathy They conclude that pre equatorial cells synthesize a fibrillar protein in most aging persons and that the excessive production of this protein results in the condition known as fibrillopathy exfoliative or pseudo exfoliative disease

Most of the previous investigations have been carried out on microscopic sections This present work has been designed to study the deep layer of the anterior lens capsule in flat whole mount preparations The aim has been to investigate the distribution and structure of this layer

Materials and methods

48 cataractous lenses have been examined 24 of these exhibited the phenomenon of fibrillopathy when examined before the operation The remaining 24 are

From the University of Bergen
Department of Ophthalmology Bergen Norway
(Head Professor Torstein I Bertelsen)

FLAT WHOLE-MOUNT PREPARATIONS OF THE LENS CAPSULE IN FIBRILLOPATHIA EPITHELIOCAPSULARIS, THE SO-CALLED SENILE EXFOLIATION OR PSEUDOEXFOLIATION

BY

TORSTEIN I BERTELSEN & JOHAN H SELAND

Abstract

Lens capsules from 48 cataractous eyes with and without fibrillopathy (exfoliation/pseudoexfoliation) have been examined in flat whole mount preparations Dark ground microscopy and phase contrast microscopy showed thread like filaments in the peripheral part of the anterior lens capsule The amount of filaments was much greater in capsules from eyes with fibrillopathy than in capsules without fibrillopathy In the pre equatorial zone discoid plaques were found in fibrillopathy capsules Their localisation and structure correspond to a deep layer which has been described earlier The findings are discussed

Key words Fibrillopathia epitheliocapsularis – senile exfoliation – pseudoexfoliation – lens capsule – deep layer – discoid plaque

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Table I
Summary of the processes to which the lens capsules have been subjected

	Fibrillopathia	Control
Treated with pepsin	7	3
Not treated with pepsin	17	21
Harris haematoxylin alum stain	1	1
Gomoris chrome haematoxylin stain	1	3
Unstained	22	20

Observations

Dark ground microscopy proved to be the most useful technique when studying the lens capsules Provided that the capsule was mounted with a coverslip one could observe filamentous structures in all the lens capsules These filaments were localized to the pre equatorial zone and were found in interrupted clusters in a 2 3 mm wide band No filaments could be found at or near the anterior pole or the posterior capsule In the control lenses filaments were relatively short (1 4 μ) with tapered ends The orientation was most often parallel to the capsular surface but with a random orientation between themselves Fibrillopathy lenses showed much longer filaments (up to 30 μ) which were often tortuous sometimes U shaped at times they appeared to be bifurcated and have interconnections The structures could be demonstrated throughout the whole thickness of the capsule from the surfa e to the capsulo epithelial border They were much more numerous in the fibrillopathia capsules

All fibrillopathia capsules both with and without coverslips showed discoid plaques in the pre equatorial zone (Fig 2) This phenomenon could not be demonstrated in any of the control capsules The discoid plaques have a characteristic distribution They do not exceed the peripheral cell border and they are distributed in a zone with a maximum width of about 1 5 mm The plaques can be seen as solitary islands or may be surrounded by other plaques either in a regular or an irregular fashion (Fig 2) Very often the plaques seem to line up and fuse along a radial axis corresponding to the peripheral cell rows (Figs 3 and 4)

The size of the plaques varies greatly Their diameter has been measured from 40 μ to 230 μ The fused row like plaques have been measured up to 400 μ along their radial axis The observations were essentially the same in capsules treated with Pepsin and the untreated capsules The changes were however more easily demonstrated in the former group Under high magni

matched control lenses without fibrillopathy All lenses were removed by cryo extraction without the use of *chymotrypsin Only* lenses removed without rupture of the capsule are included *in this study* Immediately following the extraction the lenses were *fixed in a mixture* consisting of one part glacial acetic acid and three parts absolute alcohol 24 hours later post fixation was *carried* out *in* 70 per cent alcohol and in this medium they were stored until further processing could take place Prior to the capsule mounting the lens was immersed in distilled water for a period varying from a few hours to a couple of days, depending on the capsular adhesion to the nuclear material The posterior capsule was incised and under the dissecting microscope the capsule was freed from its nucleus The capsule was hence mounted on a slide with the cellular layer uppermost Adhering cortex tissue was gently and carefully removed with a silver spatula The capsule was allowed to dry (Fig 1) Only intact capsules where at least half of the capsular surface was suitable for microscopy are *included in this study* Ten of the capsules were treated with a 0 2 per cent Pepsin solution for a period of 1/2 to 4 1/4 hours in order to remove cortical debris and some of the cellular layer



Fig 1
Flat whole mount preparation of the lens capsule

Some of the capsules were stained with Comoris chrome haematoxylin stain and Harris haematoxylin alum stain and the coverslip was mounted with Canada balsam (Table 1) Most of the capsules were however studied without further processing The preparations were subjected to ordinary microscopy dark ground microscopy and phase contrast microscopy

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fication the plaques are seen to consist of multiple light dots which often have a higher concentration in the center than in the periphery (Fig 3) Occasionally spindle shaped elongated white structures are seen

All these findings were confirmed with phase contrast microscopy This technique enchanced the visibility of the filament Phase contrast microscopy can



Fig 2
Fibrillopathia Whole mount Pepsin treated Harris haematoxylin alum stain Dark ground microscopy *Solid white arrow points to the peripheral cell border Open white* arrow shows irregular discoid plaques (Original magnification 40 times reduced [1])

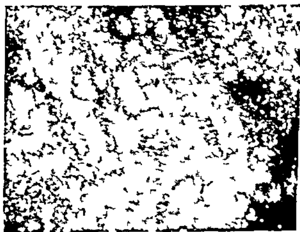


Fig 3
Fibrillopathia Whole mount Pepsin treated Harris haematoxylin alum stain Discoid plaques of various sizes Noite the tendency to line up in a radial fashion (Original *magnification 100 times reduced [1])*

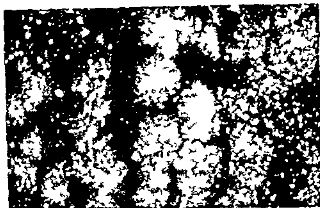


Fig 4
Fibrillopathia. Whole mount Untreated unstained Dark ground microscopy Discoid plaques (Original magnification 200 times reduced 1/3)

only be carried out on capsules provided with a coverslip Fig 7 shows a plaque studied with phase contrast microscopy When focusing near the cellular layer the plaque is depicted as dot like stippling (Fig 7 a) When changing the focus some μ nearer the capsular surface the stippling is replaced by spindle shaped filaments (Fig 7 b) Ordinary microscopy did not add anything to the above mentioned observations

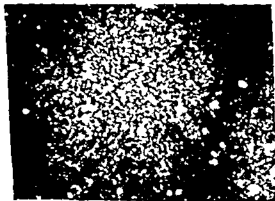


Fig 5
Fibrillopathia Whole mount Untreated unstained Dark ground microscopy The bundles of fibrils in the deep layer appearing as white dots and filamentous structures. (Original magnification 400 times reduced 1/3)

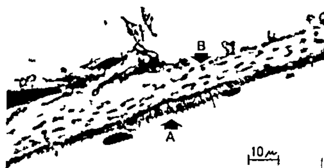


Fig 6

Section of the anterior lens capsule near the equator Fibrillopathia Pepsin treated Harris haematoxylin alum stain Phase contrast Note the brush like deep layer (A) Note also the filaments in the proper capsule (B)

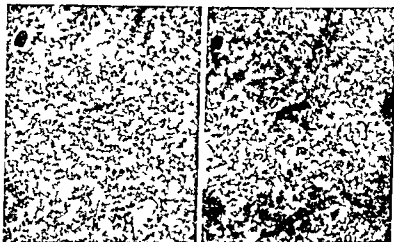


Fig 7

Fibrillopathy Whole mount Pepsin treated Harris haematoxylin alum stain Phase contrast Discoid plaque of deep layer a Focus near the cellular layer The bundles of fibrils in the deep layer appearing as small black dots b Focus altered 3 μ into the proper capsule Note that the dotted appearence of the deep layer has disappeared and is replaced by filamentous dark structures (Original magnification 200 times reduced 1/)

Comments

There seems to be no doubt that the discoid plaques found in the peripheral part of the anterior lens capsule of fibrillopathy lenses represent the deep layer of the lens capsule as described earlier (Bertelsen Drablos & Flood 1964 Ashton 1965) The plaques correspond both in localisation and morphology to this structure In the deep layer bundles of fibrils radiate out from pits and

epithelial surface membrane and these fibrils are orientated vertically into the capsular surface (Fig 6) In whole mounts they are seen end on and therefore appear like small dots (Figs 5 and 7 a)

The filaments found in the peripheral part of the proper capsule correspond to the dots clefts and patches seen in sections as described earlier (Bertelsen Drablos & Flood 1964) (Fig 6) These filaments are usually more abundant superficial to a discoid plaque As the bundles of fibrils from the deep layer gradually become incorporated in the proper capsule they change their orientation to be more or less parallel to the capsular surface They therefore appear as filaments in whole mounts Filaments may also be found in the proper capsule in between the discoid plaques of deep layer These can be explained either by some degree of movement caused by growth or perhaps more likely that the deep layer is a temporary structure appearing and disappearing throughout the plaque zone The filaments of the proper capsule of lenses without fibrillopathy have been described previously by Monahan (1953) and Dark (1961) Dark Streeten & Jones (1969) have shown that even epithelial cells of such lenses produce fibrils which radiate out from their surface membranes The theory put forward by the latter authors that the difference between normal and fibrillopathy lenses is probably one of quantity is not inconsistent with the present findings The production of fibrils in fibrillopathy lens capsules is of such a magnitude in the pre equatorial zone that aggregations occur in form of discoid plaques in a deep layer

Postulating a transport system from the epithelial cells to the surface one can explain the appearence of abnormal filaments in the proper lens capsule and Busacca bushes on the peripheral part of the anterior surface It is however also conceivable that a more low grade production of fibrils takes place even in the metabolically relatively inactive central epithelial cells If this is so fibrillopathia material appears on the whole of the anterior capsular surface The iris action produces a clear intermediate zone leaving a central disc intact Electronmicroscopic work is in progress along these lines

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Author s adress
Haukeland Sykehus 5000 Bergen Norway

HEMIATROPHIE FACIALE PROGRESSIVE AVEC MEGALOCORNEE, MICROPAPILLE ET DYSTROPHIE NUAGEUSE CENTRALE DE LA CORNEE

PAR

MICHEL COLLIER

La présence d anomalies de developpement chez des sujets atteints de syndrome de Romberg est rare Elle n est cependant pas illogique

Si," a dit Franceschetti (1952) a première vue l association d une anomalie congénitale avec une dégenerescence tardive du type de l hémiatrophie faciale peut surprendre il faut cependant se rappeler que les hérédo dégénérescences (myasthenie hérédo ataxie, syringomyélie etc) s accompagnent souvent d anomalies constitutionnelles ou de malformations congénitales C est pour quoi la rencontre d une mégalocornée bilaterale et d une micropapille unilaterale dans le cas que nous allons rapporter nous a paru intéressante

D autre part la présence d une dystrophie cornéenne chez ce meme sujet ne nous a pas surpris car nous l avions deja relevée dans une précédente étude (Collier 1960) ou il s agissait aussi d une dystrophie nuageuse centrale du parenchyme corneen De meme nous avions deja signale en 1967 un cas d hémiatrophie faciale avec micropapille (Collier 1967)

La rencontre de memes anomalies soit de développement (micropapille) soit de degénerescence (dystrophie corneenne) chez plusieurs sujets porteurs de la meme hérédo degénerescence rare (syndrome de Romberg) ne nous a pas paru fortuite et justifie pensons nous le rapport du cas suivant

Observation

M M Charles 75 ans nous consulte le 26 juin 1971 pour vérification de ses lunettes L acuité visuelle est a l oeil droit de 4/10 améliorés a 9/10 par

Reçu Juillet 22 1971



Figure 1
Mèche médio frontale blanche Syndrome de Claude Bernard Horner Pseudo-lèvre double traumatique



Figure 2
Hemiatrophie faciale progressive droite avec disparition de la boule de Bichat et attraction vers le haut de la commissure labiale Alopecie fronto temporale

+0 50 L oeil gauche qui serait amblyope de longue date voit 1/10 avec +° Cet oeil se presente d ailleurs en légere divergence

Il existe a gauche un petit syndrome de Claude Bernard Horner enophtalmie retrecissement de la fente palpebrale miosis (Fig 1)

Le tonus oculaire est de 22 a l aplanation a l oeil droit et de 17 a l oeil gauche Les champs visuels sont normal a droite concentriquement retreci a gauche d une façon harmonieuse Il n existe pas d hespéranopie

La reflexie pupillaire est satisfaisante ainsi que la musculature extrinseque des globes oculaires La sensibilite cornéenne est subnormale a l esthésiomètre de Bonnet et Cochet La vision des couleurs au Panel D 15 est bonne

L examen biomicroscopique montre au niveau des cornées mais d une façon plus marquée a la cornée droite une dystrophie nuageuse centrale surtout posterieure (Fig 4)

Les cristallins sont le siège surtout a gauche de cataractes coronaire et céruléenne

L ophtalmoscope révele aux deux fonds d oeil une sclerose etendue des vaisseaux choroidiens Cette sclérose a deja ete observée dans le syndrome de Romberg (Redi & Magri 1965) Les papilles ont un aspect pseudo glaucomateux et en outre la papille gauche est reduite en dimension des deux tiers environ par rapport a la droite (Fig 6) Elle est en outre entouree d un cercle



Figure 3
Hemiatrophie faciale probable mais modifiee par une blessure du maxillaire inferieur gauche

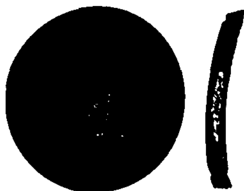


Figure 4
Dystrophie nuageuse centrale de J François

blanc particularité que nous avons souvent constatee chez les porteurs de meche frontale blanche

Le faciès de ce sujet est remarquable pour deux raisons il existe a gauche (Fig 3) une longue cicatrice cervico maxillaire par blessure de guerre le projectile ayant interesse la machoire et etant ressorti a l union des deux moities de la levre superieure determinant un aspect de pseudo levre double (Fig 1) Il est difficile de préciser si le processus d hemiatrophie faciale est en question du cote gauche de la face mais il est patent a droite (Fig 2) ou la boule de Bichat a disparu et ou la commissure labiale est attiree vers le haut



Figure 6
Micropapille gauche Sclérose des vaisseaux choroidiens



Figure 5

Mégalocornée droite (14 mm) Interruption de la marge ciliaire supérieure à l'union de ses 2/3 externes et de son 1/3 interne qu'on retrouve selon une ligne oblique en dehors à la paupière inférieure avec changement de direction des cils

Il existe de ce côté des troubles phanériens pousse très discrète de la barbe et quelques troubles sudoraux

On note une alopécie en plage temporo-frontale bilatérale et une mèche blanche frontale apparue vers l'âge de 20 ans deux ans avant la blessure de guerre et au moment où l'hémiatrophie faciale s'est exagérée ce que nous avons pu contrôler par l'examen de photographies d'identité Il n'existe pas d'alopécie sourcilière ou ciliaire

La dimension des deux cornées est de 14 millimètres (Fig 5) A droite à l'union des 2/3 externes et du 1/3 interne de la marge ciliaire interruption des cils qu'on retrouve plus visible à la paupière inférieure selon une ligne oblique en dehors avec changement de direction des cils Il est possible qu'il s'agisse d'un équivalent minime de "coup de sabre de la face Il n'y a pas d'hétérochromie irienne

L'état général est excellent et les examens biologiques de routine sont normaux Il n'y a pas d'hémiatrophie dimidiée ni croisée ni de spedatrophie

Commentaires

1° Nous éliminons le symptome *lèvre double qui est ici peu marqué et d'origine* certainement traumatique Nous avons rencontré ce signe dans un cas (Collier 1967) avec micropapille gauche et cyclite hétérochromique de Fuchs

lui aussi d origine traumatique Ce signe dans ces deux cas est sans relation avec le syndrome de Laffer Ascher affection dont nous avons pu examiner deux cas (Collier 1962 b) et qui a eté particulierement bien etudiee dans ses rapports avec la sclérodermie en bande le blepharochalazis de Fuchs et l hémiatrophie faciale progressive par Orlowski et collaborateurs Ces auteurs, apres avoir esquissé une théorie de tendance unciste (1963 a) pour les syndromes de Romberg et d Ascher ont conclu ulterieurement (Orlowski et al 1963 b) que les examens electro myographiques ne permettaient pas de differencier les diverses maladies atrophiantes de la face mais qu ils ne permettaient pas non plus de conclusions sur une etio pathogenie commune a ces diverses maladies

En 1961 nous avons rapporte un cas mixte ou étaient associes un coup de sabre frontal avec hypoplasie faciale une dysostose mandibulo faciale avec orifice auriculaire borgne appendices juxta auriculaires et une hypoplasie papillaire (Collier 1961) La rencontre d une micropapille dans trois cas d hémiatrophie faciale nous amene donc a discuter cette seconde association pathologique

2° Nous avons défini en 1960 (Collier & Adias 1960) un cadre clinique comprenant la *micropapille* (diminution harmonieuse des dimensions papillaires) des troubles perimetriques un ensemble de petites anomalies faciales et meme squelettiques (Collier 1962 a) une amblyopie des troubles intellectuels et de nombreuses anomalies congénitales des fonds d oeil Le caractere familial de ces micropapilles est maintenant bien connu (Collier & Adias 1960 Collier 1962 a) En comparaison avec les mégalopapilles qui peuvent se trouver associees dans une meme famille avec les micropapilles (Collier 1962 a) nous supposons avec Badtke qu il est possible d etablir une serie tératologique allant du colobome a l entree du nerf optique jusqu a la papille aplasique en passant par les intermediaires megalopapille papille normale papille hypoplasique La base commune de ces malformations serait une anomalie embryonnaire de la papille epithéliale primitive Une de nos observations associant megalopapille et colobome choroidien autorisait a inclure les troubles colobomateux dans cette serie teratologique

Streiff et collaborateurs (1955) ont rapporte la coexistence d un colobome de l uvée et d hémiatrophie faciale progressive D autres auteurs (Marakis 1964) ont rapporte l association cataracte congénitale homolaterale Ces associations etaient déja pour Wartenberg un argument en faveur d une pathogénie herédo dégénérative de la maladie de Romberg

3° L association supplémentaire dans notre cas present d une autre anomalie congénitale dimensionnelle du globe oculaire *la mégalocornee* nous parait renforcer encore cette théorie

C est la premiere fois qu elle est décrite en association avec l hemiatrophie faciale progressive

Il ne semble pas que la megalocornée ait éte rencontree dans d autres affections atrophiantes de la face.

Par contre elle a été signalee dans quelques syndromes osseux dermatologiques neurologiques

Syndromes dermatologiques poikilodermie congenitale (Heidensleben 1960) meche frontale blanche (observation personnelle) chaine allergique (observation personnelle) etc

Syndromes osseux oxycephalie (Kayser 1939) synostose cranienne (Calamandrei 1950) *Marfan* (*Fonseca* 1946 Rados 1942 Thaden 1929 Stephenson 1945 Weve 1931) spondylarthrose (Appelmans & de Niel 1950) en transition avec les syndromes dermatologiques *dans un cas de laxite articulaire* avec atrophie musculaire

Syndromes neurologiques Parkinson avec paralysie faciale familiale (Franceschetti Appelmans) myopathie (Blum 1949) surdite avec diabete (Posthumus 1939)

L association d une mégalocornee dans notre cas avec une dystrophie cornéenne n est pas pour surprendre Cette anomalie dimentionnelle est souvent *accompagnée d anomalies corneennes* anomalie de Peters keratocone posterieur (observation personnelle) keratocone anterieur arcus juvenile (Mann *Appelmans et al 1950 Rud 1960) opacite semi lunaire perilimbique de la* Bowman (Berliner) hypertrophie des nerfs corneens (Rud) La melanose oculaire est souvent citee corneenne (Rud) face posterieure de la cornee (Kadlecova 1959) fuseau de Kruckenberg (Mann Cameron 1941) Appelmans a noté un trouble en damier du stroma posterieur et Veil & Sarrazin (1939) des vergetures des fissures de la membrane (Streiff 1949)

Des dystrophies d étiologie connue peuvent lui etre associees gargoylisme dystrophie unique (observation personnelle) et meme des dystrophies apparemment primitives comme la dystrophie en mosaique soit posterieure (Rud) soit antérieure (Boles Carenini 1961 Young 1968) *Dans ces derniers cas* les deux affections sont familiales (Boles Carenini 1961 Young 1968)

4°-*L association de la maladie de Romberg avec la dystrophie nuageuse centrale* de J Francois (1956) n est pas pour nous étonner car nous l avons *deja rencontrée dans* un cas d hémiatrophie faciale progressive avec syndrome de Georgiades (cataracte hypochromie) (Collier 1960)

Cette dystrophie cornéenne est herédo familiale Elle peut etre associee familialement a *la dystrophie mouchetée du parenchyme corneen* et parfois meme sur le meme sujet (Collier 1964) Elle peut aussi etre associée familialement à la *dystrophie ponctiforme predescemetique* (Collier 1965 a b) Enfin cette dystrophie que J Francois n a jamais rencontree en association avec quelque affection a éte signalée par Bietti (1965) dans un syndrome *arachnodactylie micro pherophakie* par nous memes dans un *syndrome d elastorrhexis systematisee* (Groenblad Standberg) (Collier 1965 b) et deux fois dans

une *hémiatrophie faciale progressive* Toutes ces associations pathologiques à la dystrophie nuageuse centrale nous paraissent d un grand intérêt

A part les troubles par ectropion et la kératite neuroparalytique (Franceschetti & Koenig 1952) il a été decrit une dystrophie en bandelette avec kératite bulleuse et augmentation des immunoglobulines (IgA) par Grayson & Pieroni (1970)

Resumé

Rapport d un cas d hémiatrophie faciale progressive chez un sujet porteur d une mégalocornée bilaterale d une micropapille gauche avec sclérose étendue des vaisseaux choroidiens et d une dystrophie nuageuse centrale de la cornee plus marquee a l oeil droit Si c est la premiere fois que la megalocornée est signalee dans la maladie de Romberg il n en est pas de meme de la micropapille et de la dystrophie nuageuse centrale qui ont deja été décrites par l auteur dans la meme affection

Ces anomalies de developpement ou de dégenerescence semblent confirmer l aspect herédo degenératif de l hémiatrophie faciale progressive

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Résumé

Rapport d'un cas d'hémiatrophie faciale progressive chez un sujet porteur d'une mégalocornée bilatérale, d'une micropapille gauche avec sclérose étendue des vaisseaux choroïdiens et d'une dystrophie nuageuse centrale de la cornée plus marquée à l'oeil droit. Si c'est la première fois que la mégalocornée est signalée dans la maladie de Romberg, il n'en est pas de même de la micropapille et de la dystrophie nuageuse centrale qui ont déjà été décrites par l'auteur dans la même affection.

Ces anomalies de développement ou de dégénérescence semblent confirmer l'aspect hérédo-dégénératif de l'hémiatrophie faciale progressive.

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Aus der Univ.-Augenklinik Greifswald
(Direktor: Professor Dr. G. Günther)

PUPILLOMOTORISCHE VERANDERUNGEN BEI DIABETIKERN

VON

H. GLIEM

Obwohl die Morphologie diabetogener Schadigungen von Muskulatur und Pigmentepithel der Iris gut bekannt ist, sind die Meinungen uber die Funktion der Pupille *viel weniger einhellig. Einige Autoren sprechen von einem* herabgesetzten Lichtreflex wie Elschnig (1929), Groenouw (1904), Car (1925), Whittington und Lawrence (1958) und weisen zumeist gleichzeitig auf die schlechte medikamentose Erweiterungsfahigkeit der Pupille bei Diabetikern hin (Braun 1937, Dardenne 1966, Janert 1958). Wahrend Friedman et al. (1967) die verlangsamte Lichtreaktion als Ausdruck der diabetischen Neuropathie ansehen, negieren andere Neurologen (Feudell 1963, Gibbels und Schliep 1970) eine gesicherte Beeintrachtigung der Pupillenfunktion durch die Zuckerkrankheit. *Diese Auffassung wird bestarkt durch die geradezu als charakteristisch hervor*gehobene intakte Pupillomotorik bei diabetogenen Oculomotoriusparesen (Eareckson und Miller 1952, Rucker 1958, Zorilla und Kozak 1967). Diese Widersprüchlichkeit der Meinungen wird z. T. dadurch verstandlich, dass objektive Messungen bislang fehlten. Lediglich Janert und Kiebittel (1958) griffen auf die pupillographische Methode von Drischel zuruck, um die Pupillodynamik des Diabetikers exakt zu untersuchen. Aus methodischen Grunden konnten sie keine Aussagen zur Weite und Grossenanderung der Irisblende machen, ermittelten aber eine gesicherte Verkurzung der Latenz und der Kon-

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Adresse de l auteur
Dr M Collier 26 rue Servier (64) PAU France.

Untersuchungsgangen

Nach 15 min dauerndem Aufenthalt im verdunkelten Untersuchungsraum wurde die Ausgangsweite der Pupillen photographisch fixiert wobei der Kopf der Versuchsperson auf einer ublichen Kinnstutze gelagert war und ein 5 m entfernter roter Lichtpunkt fixiert wurde Nach der Ausrichtung der photo elektrischen Adapter auf beide Augen die gleichzeitig die Beleuchtung der Irides mit Infrarotlicht besorgen wurde eine *Pupille mit der hochsten Inten sitat* stimuliert und der Reflexablauf registriert Danach wurde die Zeit zwi schen Reizbeginn und dem Kontraktionsmaximum der Pupille ausgemessen und am Zeitverzogerer des zur Photographie dienenden Blitzlichtes eingestellt Bei dem nunmehr wiederholt mit gleicher Reizintensitat ausgelosten Licht reflex wird die Pupille zum zweiten Male – jetzt wahrend des Kontraktions *maximums – photographiert Nach der Entwicklung des Filmes im Anschluss* an die Gesamtuntersuchung wird die Pupillenwerte an Hand eines mitphoto graphierten Massstabes gemessen und die Kontraktionsamplitude auf den ver wendeten Reiz bestimmt Dieser Wert dient dazu die Oszillographenausschlage aller Einzelversuche in die wirkliche Pupillenweite umzurechnen Nach der Stimulation mit Einzelreizen in vier Intensitatsstufen folgten die weiter unten *naher zu beschreibenden Doppel und Flimmerbelichtungen*

Ergebnisse

Die *Ausgangsweite* der Pupillen nach dem Dunkelaufenthalt betrug im Mittel bei der Normgruppe 6 , mm bei den Diabetikern mit Erkrankungsdauer unter 20 Jahren 6 2 mm und bei denen uber 20 Jahren Diabetesdauer 5 4 mm

Da zwischen direkter und konsensueller Antwort keine Unterschiede be t nden wurden beide Werte fur die Ermittlung der *Reflexamplitude nach Fin elrei en* verwendet Es wurde mit der erniedrigten Intensitat begonnen

Tab 1

Mittlere Reflexamplitude in mm Reizintensitat

	10^{-3}	10^{-}	10^{-1}	10
Normgruppe	0 83	1 4	1,57	2 05
Diabetiker insgesamt	0 6	1 01	1,32	1 60
Diab uber 0 J DD	0,55	0 ,8	1 14	1 0

traktionszeit die auffälligerweise bei Probanden mit kurzer Diabetesdauer besonders deutlich war

Somit erschienen uns eigene pupillographische Untersuchungen gerechtfertigt

Untersuchungsmethodik

Die von uns verwendete sog „dynamische Pupillographie wurde an anderer Stelle (Kietzmann und Gliem 1971) ausführlich beschrieben so soll hier nur kurz auf das Prinzip der Methode eigegangen werden Es beruht auf der bewährten photoelektrischen Registrierung des von der Iris reflektierten infraroten (pupillomotorisch inaktiven) Lichtes durch eine Photodiode (Matthes Drischel) Die von dieser erzeugte Spannung ist der Reflektionsfläche (also der Iris) proportional Es lässt sich auf diese Art nur der Ablauf der Pupillenreaktion aufzeichnen Aussagen uber die Pupillenweite sind nicht moglich Diesen Nachteil haben wir dadurch aufgehoben dass wir mit Hilfe einer photographischelektronischen Ergänzung den Pupillendurchmesser vor und nach dem Lichtreiz aufzeichneten So wurde es möglich die Amplitude des Lichtreflexes in mm auszumessen und diesen Wert als Bezug fur alle folgenden Registrierungen zu verwenden Das Reizlicht kann in seiner Intensität durch Neutralfilter in vier logarithmischen Stufen und in seiner Dauer sowie Folge durch einen elektronischen Reizgeber (Foto Fono Stimulator FS 4 VEB TuR Dresden) stark variiert werden Zur Registrierung der Spannung der Photodiode diente ein Elektro Encephalograph (VEB Messgerätewerk Zwonitz) und ein Zweistrahloszillograph (Duoskop VEB Technisch Physikalische Werkstätten Thalheim)

Probanden

Die zum Vergleich dienende Normgruppe besteht aus 25 Augen und Stoffwechselgesunden (50 Augen) und einem Durchschnittsalter von 30 Jahren Ihr wurden die Ergebnisse von 52 Diabetikern (104 Augen) gegenubergestellt Sie wurden uns bis auf wenige Ausnahmen vom Zentralinstitut fur Diabetes Karlsburg (Dir Prof Dr H Bibergeil) überwiesen Diese Gruppe hatte ein mittleres Lebensalter von 40 Jahren die Erkrankung begann durchschnittlich bei ihr im 21 Lebensjahr so dass die mittlere Diabetesdauer 19 Jahre betrug 4 der Patienten wiesen keine Retinopathie (R) auf 8 eine R I (Mikroaneurysmen und punktformige Blutungen) sowie 10 eine R II (zusatzlich Exsudate) Die ubrigen Probanden zeigten unterschiedliche Grade proliferativer Veranderungen am Fundus (R III)

Tab III

Kontraktionszeitmittelwerte in msec Reizintensitat

	10^{-3}	10^{-2}	10^{-1}	10
Normgruppe	250	300	350	3[illegible]0
Diab bis zu 10 J DD	[illegible],0	300	320	380
Diab uber 10 J DD	2,0	290	370	360

kungsdauer und den ubrigen zum Ausdruck kommen als gesichert gelten Eine Haufigkeitsverteilung der Einzelwerte bestatigte die allgemeine Erniedrigung der Latenzzeit bei kurzer Diabetesdauer gegenuber den Stoffwechselgesunden denn 80–100 % der Messungen lagen bei ihnen unter dem jeweiligen Mittelwert der Norm

Unter der Kontraktions eit des Lichtreflexes verstehen wir die Dauer der Pupillenverengerung bis zu ihrem Maximum Die Messungen sind wiederum mit einem gewissen Fehlen behaftet da die Kontraktion langsam beginnt und bei Annaherung an den Gipfel wieder allmahlich gebremst wird so dass sich Anfang und Ende des Vorganges nicht immer ausreichend genau bestimmen lassen Wie von anderen Autoren beschrieben wurde (Loewenstein und Loewenfeld) verhalt sich die Kontraktionszeit umgekehrt wie die Latenzzeit und erfahrt mit zunehmender Reizintensitat eine wesentliche Verlangerung

Die Mittelwerte der Kontraktionszeiten in der Tab II weisen in beiden Diabetikergruppen keine Unterschiede gegenuber der Norm auf Ebenso konnten wir bei der Haufigkeitsaufschlusselung der Einzelergebnisse keine sichere Entwicklungstendenz in dieser oder jener Richtung bemerken Die Werte verteilen sich mit annahernd gleicher Zahl um die angegebenen Mittel

Wenn das Ausmass der Pupillenverengerung (die Reflexamplitude) bei Diabetikern herabgesetzt ist die Dauer des Vorganges (Kontraktionszeit) aber unverandert bleibt so muss sich das in einer verminderten *Geschwindigkeit des Lichtreflexes* ausdrucken (s Tab IV)

Tab IV

Reflexgeschwindigkeit in mm sec Reizintensitat

	10^{-3}	10^{-2}	10^{-1}	10
Normgruppe	3 5	4 07	4 32	5 [illegible]
Diab bis zu 10 J DD	[illegible] 0	3 48	4 1[illegible]	5 00
Diab uber 10 J DD	03	[illegible] 63	3,[illegible]6	4 [illegible]

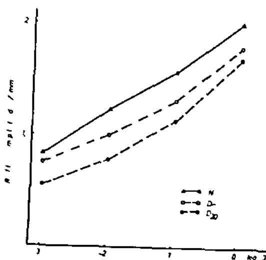


Abb 1
Reflexamplitude auf 4 Lichtreize ansteigender Intensitat (Mittelwerte der Normgruppe (N) der gesamten Diabetikergruppe (DC) und der Diabetiker mit einer Erkrankungsdauer uber 20 Jahren (D o))

die Reizdauer betrug 100 msec Sowohl bei den Gesunden als auch bei den Diabetikern stieg unter den geschilderten Bedingungen die mittlere Reflex amplitude in fast linearer Abhängigkeit vom Logarithmus der Reizintensitat an (s Abb 1 und Tab I)

Die Unterschiede zwischen der Vergleichs und der Diabetikergruppe sind statistisch gesichert (t Test)

Die Laten eit des Lichtreflexes (vom Einsetzen des Reizes bis zum Beginn der Pupillenverengerung gemessen) nimmt mit zunehmender Intensitat ab Die in Tab II angegebenen Mittelwerte sind auf bw abgerundet und zudem mit einer relativ hohen Streubreite behaftet da sich der Anfang der Kontraktion nicht in erwunschtem Masse exakt definieren liess Trotzdem konnen die Unter schiede die zwischen der Normgruppe den Diabetikern mit kurzer Erkran

Tab II
Latenzzeitmittelwerte in msec Reizintensitat

	10-3	10	10 1	10°
Normgruppe	380	2 0	250	?40
Diab bis zu 10 J DD	280	260	220	180
Diab uber 10 J DD	340	320	?80	-60

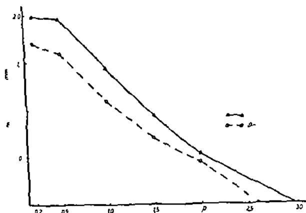


Abb 3
Amplitude der Pupillenoszillationen der Flimmerbelichtung in Abhangigkeit von der Reizfrequenz
(N = Normalgruppe Dg = gesamte Gruppe der Diabetiker)

um mit der Verkurzung der Reizfolge dann rasch abzunehmen Bei 3 Hz wurde im Mittel die Flimmerfusionsfrequenz erreicht Die Oszillationen der Diabetikergruppe waren wahrend der gesamten Versuchsfolge signifikant kleiner folgten aber sonst dem Grossenabfall der Normgruppe und erreichten die Fusionsgrenze schon bei 2 6 Hz (s Abb 3) Patienten mit einer Diabetesdauer uber 20 Jahren wichen bis auf die Flimmerfusionsfrequenz von 2 5 Hz hiervon nicht ab

Diskussion

Die beschriebenen Versuche und ihre Ergebnisse lassen folgende Feststellungen uber den Einfluss des Diabetes mellitus (oder dessen Folgen) auf die Pupille und ihren Lichtreflex zu

1 Die Erweiterungsfahigkeit der Diabetikerpupillen wahrend eines Dunkelaufenthaltes ist ebenso wie ihre Reaktion auf Mydriatika herabgesetzt und wird stark durch die Diabetesdauer beeinflusst Obwohl neuerdings durch Loewenfeld und Newsome (1971) eine mechanische Begrenzung der Pupillomotorik durch die Blutgefasse der Iris nicht gefunden werden konnte muss noch dahingestellt bleiben ob hier ausschliesslich muskulare Ursachen wirksam werden oder ob nicht die uberhohte Rigiditat der Gefasse von longterm Diabetikern die normale Erweiterung der Pupille im Dunkeln behindert

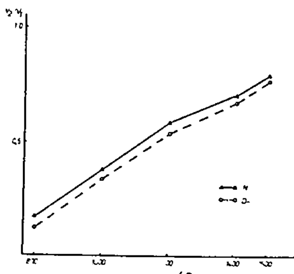


Abb 2
Verhaltnis der 2 zur 1 Reflexamplitude bei Doppelreizen mit unterschiedlichem Intervall
(N = Normalgruppe D_G = gesamte Gruppe der Diabetiker)

Um das *Reflexverhalten nach Doppelreizen* zu prüfen wurden die Pupillen Belichtungen grösstmöglicher Intensität und einer Dauer von 70 msec aus gesetzt Der Abstand zwischen zwei derartigen Reizen wurde von 800 auf 1500 msec langsam gesteigert das Intervall zwischen einer solchem Doppel blitzgruppe mit 5 sec aber konstant gehalten Unterhalb von 800 msec Reiz abstand konnten wir keine Reaktion auf die zweite Stimulation in der Gruppe registrieren Die nach diesem Grenzwert auftretende Antwort vergrosserte sich zwar rasch mit dem zunehmenden Abstand zwischen den Belichtungen blieb aber innerhalb des angegebenen Bereiches stets kleiner als der jeweilige erste Reflex In der Abb 2 ist das Verhaltnis der 2 zur 1 Reflexamplitude (V_2/V_1) in Abhängigkeit vom Reizintervall dargestellt Obwohl der Unterschied zwischen Norm und Diabetikergruppe nur gering erscheinen mag ist zu berücksichtigen dass durch die Quotientenbildung Messfehler eliminiert und die Streubreiten verringert wurden Dadurch liess sich die Erniedrigung der Mittelwerte aller Diabetiker statistisch gut sichern (t Test P = 0 01 %)

Mit der vorhandenen Methodik konnten die *Pupillenreaktionen auf Flimmerreize* zwischen 0 2 und 6 Hz gepruft werden Der jeweilige Einzelreiz hatte den Charakter eines Rechteckimpulses von 70 msec Dauer mit der hochst möglichen Intensitat Wie Loewenstein und Loewenfeld (1969) zeichneten wir bei niedrigen Reizfrequenzen noch Pupillenoszillationen auf die mit steigender Hz Zahl kleiner wurden Bei Reizintervallen zwischen 5 sec (0 2 Hz) und 2 sec (0 5 Hz) wiesen diese bei den gesunden Probanden noch das beschriebene mittlere Ausmass der Reflexamplitude von 2 mm nach Einzelstimulationen auf

Sofortadaptation und Erhohung der Blendenempfindlichkeit sowie der diabetischen Lentopathie beitragen die Leistungsbreite des Auges einzuschranken Das scheint uns insofern beachtenswert weil Patientengruppen betroffen werden konnen bei denen die Insulinsubstitution sonst eine umfassende Wiedereingliederung in das soziale und okonomische Umweltgefüge ermoglicht

Zusammenfassung

Pupillographische Untersuchungen bei Diabetikern ergaben eine verminderte *Erweiterung der Pupillen im Dunkeln eine herabgesetzte* Lichtreflexamplitude eine Verkurzung der Latenzzeit des Reflexes bei Patienten mit kurzer Erkrankungsdauer einer normale Kontraktionszeit sowie eine verminderte Reaktion auf Doppel und Flimmerreize

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2 Bei der durch eine geringere Pupillenweite gekennzeichneten Ausgangssituation führt die Belichtung zu einer geringeren Kontraktion des Irisdiaphragmas als bei gesunden Probanden Diese verminderte Reflexamplitude fällt bei längerem Bestand der Zuckerkrankheit stärker ins Gewicht Trotz dieses eindeutigen diabetogenen Einflusses auf die Pupillomotorik wird er ohne objektive Registrierung nicht deutlich, da die geringere Ausgangsweite verbunden mit der herabgesetzten Reflexamplitude bei der einen Gruppe und die weitere Pupille zusammen mit der ausgiebigeren Belichtungsantwort bei der anderen zu einem *ähnlichen Reizerfolg also zu einer gleichen Blendenweite auf der Höhe des Kontraktionsmaximums führt*

3 Gleichstarke Lichtreize bewirken bei Diabetikern und Gesunden eine gleichlange Kontraktionszeit Die herabgesetze Reflexamplitude bei den ersteren die kürzere Wegstrecke die in derselben Zeit zurückgelegt wird führt dazu *dass der Reflexablauf bei Zuckerkranken verlangsamt ist* Auf diese Weise kann die oft zu beobachtende „reflektorische Pupillenträgheit erklärt werden Nebenbei ist hier auf die bislang noch nicht beschriebene Steigerung der Reflexgeschwindigkeit hinzuweisen die wir mit der Erhöhung der Reizintensität feststellten Es scheint sich dabei um ein allgemeines Charakteristikum des pupillomotorischen Systems zu handeln Den raschen Bewegungsformen der extraokularen Muskulatur (z B den Blickbewegungen oder der raschen Nystagmusphase) liegt die gleiche Gesetzmässigkeit inne längere Strecken durch eine höhere Beschleunigung zu überwinden

4 Die Untersuchungen der Belastbarkeit der Pupillomotorik durch kurz aufeinanderfolgende Doppelreize oder durch Flimmerbelichtung zeigten dass die Diabetikerpupille der von Gesunden deutlich unterlegen ist Die Blendenfunktion des Irisdiaphragmas mit dem regulatorischen Ziel die retinale Belichtung auch bei schnellem Wechsel der äusseren Bedingungen konstant zu halten ist bei Diabetikern eingeschränkt Weitere Untersuchungen müssen angestellt werden um die Rolle der Phasenverschiebung zu ermitteln

5 Von besonderem Interessen dürfte die Latenzzeitverkürzung bei Diabetikern mit kurzer Erkrankungsdauer sein Sie könnte ebensogut lokalen Ursprungs wie ein Korrelat der erhöhten Nervenleitgeschwindigkeit sein die elektromyographisch bei der motorischen Form der Neuropathia diabetica registriert wurde Weder die Latenzzeit noch die anderen Erhebungen waren bei den Diabetikern vom Ausmass der Fundusveränderungen abhängig

Die pupillomotorischen Veränderungen des Diabetikers dürften praktisches Interesse beanspruchen da sie zusammen mit den anderen Manifestationsformen der Krankheit am vorderen Augenabschnitt wie den transitorischen Refraktionsänderungen den Akkommodationsstörungen der Herabsetzung der

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It has been well accepted that direct gonioscopy using a Koeppe lens is the most satisfactory method of gonioscopy because this provides the least distorted and clearest image of the angle (Chandler & Grant 1965 Shaffer 1962) It seems desirable therefore to have a type of direct gonioscopy designed to reveal the details of the hidden structures of the narrow angle

The purpose of the present communication is to report on a new direct gonio lens devised by the authors which uses corneal indentation to widen the chamber angle

The Structure of the Lens

The goniolens to be described is in principle a modified Koeppe lens (Fig 1) The concave surface which is shown in Fig 2a faces the cornea The upper surface is domed in shape In order to modify the Koeppe lens a vertical section of about $^1/_4$ of the whole in size was removed from the dome Fig 2b is a lateral view of the lens illustrating this section The lower portion of our lens is a complete departure in shape from the Koeppe lens Between the vertical section and the concave surface an oblique facet has been made which intersects the vertical plane at a 135° angle (see also Fig 2b) A shallow round dimple (2 mm in diameter) has been made at the top of the dome in which a rod or a muscle hook can be fitted so that the lens can be manipulated easily The lens and the rod are made of plastic and weigh about 1 7 g The lens is currently being manufactured by the Tokyo Contact Lens Institute Hongo Bunkyo ku Tokyo Japan



Fig 1

The gon olens devised for the corneal ndentation gonioscopy ewed from side The rod s mounted to the dome shaped upper surface

The Glaucoma Service
Department of Ophthalmology (Director: Prof. Y. Suzuki)
Chiba University School of Medicine, Chiba-shi, Japan

A NEW GONIOLENS FOR CORNEAL INDENTATION GONIOSCOPY

BY

YASUHISA NAKAMURA & YOSHIAKI KITAZAWA

The importance of gonioscopy in the proper diagnosis and treatment of glaucoma cannot be overemphasized. In the narrow angle eye, however, it is often extremely difficult to obtain a detailed view of the angle hidden by the peripheral root of the iris by means of the conventional methods of gonioscopy. In particular, it is practically impossible with the conventional gonioscopic technique to distinguish the synechial closure of the angle from its appositional closure and vice versa (Shaffer 1957, Chandler & Simmons 1965).

Attempts to widen the chamber angle artificially have been made in an effort to make hidden angle structures visible. For this purpose surgical deepening of the chamber angle has been advocated by Shaffer (1957), Ogino (1961) and Chandler & Simmons (1965) independently. Although gonioscopy with surgical deepening of the anterior chamber makes it possible to assess the extent of the formation of peripheral anterior synechia (PAS) accurately, this procedure has the inherent disadvantage of requiring surgical intervention in the operating room. Forbes (1966) devised a method of corneal indentation gonioscopy in which he used a Zeiss four mirrored contact lens. His technique requires the use of a slit lamp and is essentially indirect gonioscopy.

Read at the Twenty Ninth Clinical Meeting of the Wilmer Resident Association in Baltimore on 17 April 1970.
Received August 20, 1971.

cessary to open up the angle Pushing the lens virgorously results in folding the endothelial surface of the cornea which distorts the view The magnified view of the angle can be obtained with a magnifying glass or an operating microscope

Goniophotographs

Goniophotographs taken in a patient (either with or without corneal indentation) will be presented

The goniophotographs were taken with a Kowa hand held fundus camera

The goniophotographs from a 54 year old Japanese female patient are shown in *Figs 3 and 4* The *patient* was *diagnosed to* have what appeared to be



Fig 3
Narrow anterior chamber angle (grade 2) viewed without corneal indentation.

grade 2 narrow angle at the clinic Direct gonioscopy done at the Glaucoma Service confirmed the diagnosis in each eye i e although the functional trabeculae could be seen in about ¼ of the *entire circumference* of the angle the configuration of the angle was interpreted closure possible (Fig 3) Gonioscopy with corneal indentation disclosed several small cone shaped PAS which were attached either to functional trabeculae or to the scleral *spur* in *the temporal* angle (Fig 4) No abnormality was noted in the rest of the angle

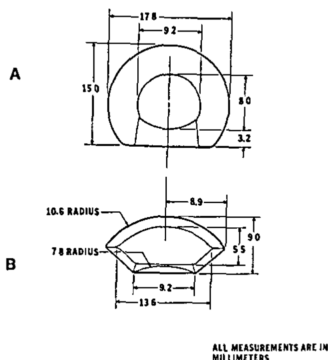


Fig 2
The structure of the goniolens

Procedure

In order to use the lens the cornea is anesthetized with 0 5 % benoxinate hydro chloride (Novesine Benoxil) Usually no solution need be put on the concave surface of the goniolens to prevent air bubbles from getting between the lens and the cornea With the goniolens placed on the center of the cornea conventional direct gonioscopy is performed while exerting only enough pressure to hold the lens in place The rod can be mounted to the lens in order to steady it as needed Corneal indentation is done in the following manner The rod is tilted towards the examiner while a gentle pressure is applied to the cornea The aqueous humor under the lens is thereby forced to move into the chamber angle and widens it This procedure can be repeated as necessary The vertical plane of the lens was made so that the upper lid does not get in the way when the upper portion of the angle is examined It is convenient to make it a rule to direct the vertical plane of the lens toward the portion of the angle which the examiner wants to see Then the vertical plane will automatically face the upper lid when the superior angle is being examined Only a minimal pressure is ne

open angle glaucoma (Pollack 1970) It is not uncommon that one encounters cases in which it is extremely difficult to decide whether or not the angle is closure possible gonioscopically Provocative tests for angle closure glaucoma can sometimes be negative even in those patients who later develop acute or subacute episodes of angle closure glaucoma (Leydhecker 1955) If the presence of PAS can be proven by means of direct gonioscopy with corneal indentation one can be confident of making the diagnosis of angle closure glaucoma Therefore it is quite conceivable that the direct gonioscopic examination reported here can help one distinguish chronic primary angle closure glaucoma from primary open angle glaucoma The importance of distinguishing primary angle closure glaucoma from primary open angle glaucoma cannot be overemphasized In the early stage of the disease process the former can be cured by relatively innocuous peripheral iridectomy (Pollack 1970 Haas & Scheie 1962) It is not rare that the failure to make a proper diagnosis results in a grave impairment of vision which could have been avoided

It is hoped that the natural course of primary angle closure glaucoma including the process of the formation of PAS can be better understood by using the method of gonioscopy reported here to follow patients with a narrow angle Such a study is currently in progress in our department

Acknowledgment

The authors are grateful to Prof Yoshitami Suzuki M D The Department of Ophthalmology Chiba University School of Medicine for reviewing the manuscript

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P lla k I D agn s s and Treatment of Angle Closure Glaucoma in Patients with



Fig 4

The same portion of the angle as shown in Fig 3 The view obtained with the corneal indentation Cone shaped synechias attaching either to a scleral spur or to functional trabecula are seen

Discussion

Our method of direct gonioscopy with corneal indentation has several distinct advantages over the methods so far devised for the purpose of examining the narrow chamber angle in detail First findings obtained by means of the direct gonioscopy with corneal indentation can be easily compared with ones obtained with conventional direct gonioscopy since the two procedures i e gonioscopy with and without corneal indentation can be performed repeatedly one after another Secondly our method does not require any surgery and can be performed at the office Thirdly as our method is essentially a modified direct gonioscopy it has all the advantages inherent in direct gonioscopy A more satisfactory view of the narrow angle can be achieved (Chandler & Grant 1965) the examination is done without a slit lamp which means that the examination is more acceptable to the patient and the gonioscopy can be performed with the eye in various positions which is sometimes desirable for observing narrow angles Fourthly the examination of the nasal and temporal angle can be done very easily Finally goniophotography can be done without difficulty Excellent photographs can be taken because no tenacious solution such as methyl cellulose is necessary to prevent air bubbles from getting under the lens

It has been pointed out that the incidence of chronic primary angle closure glaucoma is much higher than ever thought and that a significant proportion of the patients with this particular type of glaucoma are treated as primary

TRANSACTIONS OF THE SWEDISH OPHTHALMOLOGICAL SOCIETY

EDITED BY

O PALLIN Stockholm

Meeting in Stockholm Nov 30 1968

E Linner Some experiences of microsurgical trabeculotomy and trabeculectomy *ab externo* in chronic simple glaucoma (Publ in Advanc Ophthal Vol 22 pp 132 135 19 0)

Discussion by *I Anjou* The use of an operation microscope in glaucoma surgery makes possible not only new surgical procedures but also improvements of older ones The following technique has been employed at the Central Hospital in Jonkoping to obtain subconjunctival filtration

A limbus based conjuctival flap is prepared in one of the upper quadrants and an incision is made parallel to the limbus The incision is carried through sclera and cornea and enters the anterior chamber at an angle of about 45° to the perpendicular pl ne After completion of the incision a peripheral iridectomy *ab externo* is performed A 0 *u* perlon suture (a m Tubingen) is applied to both the anterior and posterior lip of the incision it is important to put the sutures exactly opposite each other in the middle of the wound The sutures are tied very firmly producing a compression of the l ps of the wound and cutting is made very close to the knots Between the suture ompressed wound edges a filtration channel is established the width of which can be somewhat predetermined by the strength applied in tying the sutures

The method described has been employed n 40 eyes with chronic simple glaucoma An I O P of less than 2 mm Hg was achieved in 85 per cent of the eyes without further therapy and in another 1? per cent by adding miotics

B J hans n Surgery f malignant tumors of the lower lid

A Ins th & L A F ansson The importance of the polysaccharides for the normal fun tion of the orn al stroma (Publ in Acta ophthal 48 3 455 19 0)

E Kock Lens ndu ed u eitis after perforating injur es

A serie of 136 eyes enucleated during the years 1963-67 because of perforating

Open Angles read at the Twenty Ninth Clinical Meeting of The Wilmer Resident Association in Baltimore April 17 1970
8 *Shaffer R N* Glaucoma Transactions of the First Conference Newell F W Editor Josih Macy Jr Foundation 1955 p13
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10 *Shaffer R N* Stereoscopic Manual of Gonioscopy The C V Mosby Co St Louis 1962 p26

Reprint requests should be sent to The Glaucoma Service Department of Ophthalmology Chiba University School of Medicine Chiba shi Japan

Case 3 Male, born in 1936 No visual complaints until the age of 31 when he had bilateral acute decrease in visual acuity Ophthalmoscopy revealed slight edema of the discs and central parts of the fundi Visual acuity when worst was counting fingers in the right eye and light perception in the left eye Neurological examination including EEG encephalography and bilateral carotis angiography was normal About one month after the onset of symptoms the discs were noticed to be pale without edema Visual acuity however had improved to 0 5 in the right eye and 0 2 in the left one. ERG and dark adaptation were normal

A diagnosis of chiasma arachnoiditis was discussed in case 3 That this diagnosis might be mistaken for Leber s optic atrophy has been reported earlier In our opinion case 3 could well be a case of Leber s disease If so it gives rise to interesting speculations on the heredity of retinitis pigmentosa and Leber s optic atrophy both of which may appear as recessive sex linked forms males generally being affected

I Rendall Mass screening of the colour vision in conscripts

H Peterson Refraction studies in a statistically representative group of Swedish conscripts

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Meeting in Gavle March 22 23 1969

Discussion on Modern trends in ophthalmo traumatology

E Kock The pathology in eye injuries and their complications

B Zetterstrom The treatment of contusion of the eye (Publ in Acta ophthal 47 3 ,84 1969)

E Palm Reconstructive surgery in injuries to the cornea and the iris

A Holmberg Injuries to the lens and their treatment

R Tornquist The vitreous and the retina in traumatology

B Knave The metalloses

B Tengroth The treatment of intraocular foreign bodies

L Berggren The treatment of infection and inflammation in perforating eye injury

---

Meeting in Stockholm Nov 29 1969

B P eng n The pathogenesis of choroidal detachment

Hypotony flat anterior chamber and choroidal detachment are complications occurring in cases with external fistulation The symptoms rapidly disappear after closing the

injury was studied histologically 83 eyes were removed because of intraocular inflammation and/or suspicion of sympathetic *ophthalmia* Twenty of these eyes (24 per cent) showed histological signs of lens induced *uveitis* whereas only one eye in the whole series showed evidence of sympathetic ophthalmia

K G Nyman & U Axelsson Side effects from use of long acting cholinesterase inhibitors in young persons (Publ in Acta ophthal 48 3 396 1970)

P Algvere & S Ervaeus Occurrence of Leber s optic atrophy and tapetoretinal degeneration *in the* same family

Leber *s optic atrophy and retinitis pigmentosa in cousins was described by* Ida Mann in 1928 No reports were found in the literature on the occurrence *of these two diseases* among children of the same family

We have studied a family with 5 children two of whom (born in 1926 and 1934) *have had* poor vision since early childhood whereas one (born in 1936) developed acute bilateral optic atrophy at the age of 31

No eye disease has been found in the parents who are first cousins among their *sisters* and brothers or in other relations The parents and their five children have *been thoroughly examined by us including* electro *retino graphy and studies of dark* adaptation

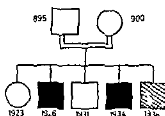


Fig 1

Pedigree of affected family Two sons had retinitis pigmentosa *(black symbols) one* developed Leber s optic atrophy (cross hatched symbol)

Case 1 Male born in 1926 At the age of two a convergent strabismus was noticed He was examined at the age of nine when optic atrophy was diagnosed in both eyes At the age of twenty five there was nystagmus pale discs very narrow vessels in the retina and also pigmentations in the peripheral parts of the fundus In 1968 when 42 years old this man was found to have a visual acuity of light perception but no projection in both eyes He had nystagmus bilateral posterior cataract and a fundus picture typical of *retinitis pigmentosa* ERG was extinguished and dark adaptation studies a m Goldmann/Weekers were pathological

Case 2 Male born in 1934 When four years old he was noticed to have pronounced difficulties in darkness *Examination by ophthalmologist revealed pale* discs narrow vessels and atrophic fundi 1968 at the age of 34 he had a visual acuity of light perception and also some projection in the right eye and counting fingers in the left eye Nystagmus was noticed Small posterior cataracts were also found *Fundus examina*tion showed pale discs narrow vessels and peripheral pigmentation ERG was extinguished and dark adaptation was pathological

the verruca as hard as possible to reduce the blood flow in it The treatment is given by freezing to −70 to −80°C during 1 minute This is repeated three times with an interval of 7–10 days The full effect complete disappearance of the verrucae without *scarring is seen* after about 6 weeks

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Meeting in Halmstad April 4 5 1970

Discussion on Neuro ophthalmology of skull injury

P Enoksson Injuries to the optic pathways

H Bynke Traumatic lesions of extraocular muscles – the mechanism of injury and early treatment

P Enoksson The Pseudo Graefe phenomenon Film

G Stigmar Some aspects on the diagnosis and treatment of post traumatic paresis of the extraocular muscles

L Ericson Blowout fractures of the orbit (Publ in Opusc med. (Stockh) 15 3/9 19 0)

E Sundmark Fractures of the zygomatic bone

Meeting in Uppsala June 6 7 1970

P Algvere Intra itreal implantation of a high molecular hyaluronic acid in surgery for retinal detachment

In surgery for retinal detachment use has been made of intravitreal injections of air physiological saline silicone oil and preparations of human vitreous Hyaluronic acid *is a fundamental* constituent of the normal vitreous and its excellent elastoviscous and optic qualities make it suitable for intravitreal injection A preparation of hyaluronic acid was produced from bovine vitreous (Etamucin Etapharm Vienna) It had a molecular weight of about 1 0 000 a viscosity of 13 centipoise but contained a considerable *amount of protein It has been used with some success but not* without considerable complications

In this study pr pa ation of high molecular hyaluronic acid have been used containing a 1 per cent solution of the Na *salt of 1 5 3 million* molecular we ght hyaluronic acid in a phy iologi al buffer (Healon, produced by E A Balazs Boston Biomedical Research Institute) The source of the hyaluronic acid was the human umbilical cord or earlier al o the rooster comb The s lution is quite transparent, having an extremely high ci ty f about 90 000 centistokes The amino acid content of th s solution is les than 0 00 per cent Since the hyaluron c acid molecules are deformable under com p c n th s luti n can be injected through a 21 or 23 *gauge needle* The preparations

fistula More frequently however the same signs appear after intraocular surgery with out the appearance of external fistulation and here the pathogenesis is obscure

In one case hypotony flat anterior chamber and choroidal detachment occurred one month after an iridencleisis On recording the tension by Schiotz tonometry the scale pointer indicated a rapid decrease interpreted as a sign of an internal passage of aqueous through the uveal vessels Therefore a silicone plomb was placed extraconjunctivally over the area of the iridencleisis fixed by sutures anchored in the sclera thus indenting the sclera After that all symptoms of the internal fistulation disappeared

I Injou Acetylcystein in keratoconjunctivitis sicca

No causal therapy is known in keratoconjunctivitis sicca This is especially troublesome in cases of the disease having filiform keratitis this complication being strongly related to the appearance of highly viscous mucus in the conjunctival sac.

The sicca syndrome and mucoviscidosis have one dysfunction in common the production of a highly viscous mucus in excretory glands

In mucoviscidosis a valuable therapy has appeared in recent years N acetyl L cystein This drug gives liquefaction of the mucus

Acetylcystein has been tried in keratoconjunctivitis sicca by Jones & Coop (1965) and Absalon & Brown (1968) These authors reported good results in their series

A series of 8 patients has been studied They all had keratoconjunctivitis sicca complicated with filiform keratitis and mucus secretion They were given acetylcystein in a 20 per cent solution (pH 7) which was applied locally in the conjunctival sac 3 4 times a day The effect was astonishingly good especially as regards the liquefaction of mucus and disappearance of filiform keratitis

B Tengroth The 4 prism test in examination of patients with strabismus

P Algvere Fluorescein studies of retinal vasculitis in sarcoidosis (Publ in Acta ophthal 48 6 1129 1970)

U Hedner M Pandolfi & I M Nilsson Bilateral occlusion of the retinal veins in a patient with inhibition of fibrinolysis (Publ in Ann Ophthal 2/5 481 484 1970)

T Jerndal Infantile congenital glaucoma in a case of ectodermal dysplasia

A boy aged one year appeared with anhidrotic ectodermal dysplasia Ophthalmological examination revealed bilateral congenital glaucoma Repeated bilateral goniotomies normalized the intraocular pressure

It can be concluded that the primary developmental disturbance affects both ectodermal and mesodermal structures Thus in patients with ectodermal dysplasia glaucoma may be suspected and gonioscopy should be performed to detect goniodysgenesis which predisposes to glaucoma

B Bengtsson Eye examinations at the medical research station at Dalby Sweden

L Wachtmeister Thermography in some eye diseases

I Rendahl Night myopia – occurrence and practical consequences

I Anjou Cryo therapy in palpebral verrucae

Verrucae situated on or near the palpebral margin are unfit for treatment with diathermy because of the effects of scarring The cryo unit by Amoils for retinal surgery has been successfully employed in a case with numerous verrucae at the lid margins

Treatment is given without local anesthesia and the cryo pencil is pressed against

the verruca as hard as possible to reduce the blood flow in it The treatment is given by freezing to -40 to -50 C during 1 minute. This is repeated three times with an interval of 5-10 days The full effect complete disappearance of the verrucae without scarring is seen after about 6 weeks

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are biologically tested on the eye of the owl monkey results being checked clinically and histologically The *sterile solution* is delivered in ampoules or syringes

During the last 10 months high molecular hyaluronic acid solutions have been injected into 11 eyes with severe retinal detachment *Nine* eyes were re operations and in the remaining two eyes hyaluronic acid was used at the first operation In all cases the injection of hyaluronic acid was made as an adjuvant to the encircling procedure according to Arruga The intravitreal injection was performed through the pars plana *As a rule* the subretinal fluid was released through a sclero choroidal perforation *1 5 2 5 ml of hyaluronic* acid solution was injected intravitreally

For various reasons all the cases treated were considered having a poor prognosis (previous operations were unsuccessful in reattaching the retina in 9 eyes) Intravitreal *injection* cured 6 of 11 cases However the successful cases have been observed for a short time only and it is not possible to evaluate their further prognosis

Healon was well tolerated and remained transparent In two eyes a transient inflammatory reaction occurred which subsided after treatment with topical corticosteroids One eye received Healon during two subsequent operations (from human and avian sources respectively) which proved successful In two cases reattachment occurred after several weeks during which time retinal tears were spontaneously sealed Massive vitreous retraction and vitreal strands showed no obvious change but in some cases the disease did not progress

Type of detachment	Number of eyes	Reattachment (number of eyes)
Giant retinal tear (equatorial dialysis)	3	2
Post traumatic (corneo scleral perforation)	2	2
Vitreous retraction and recurrent detachment	1	0
Detachment and exudative diabetic retinopathy	1	1
Vitreous hemorrhage and recurrent detachment in aphakia	1	1
Macular hole in degenerative myopia	1	0
Multiple retinal tears and degenerations in 3 4 quadrants	2	0
	11	6

R Tornquist A simple computing system for the control and follow up of patients operated for retinal detachment

S Stenkula Photocoagulation in proliferative diabetic retinopathy

S E Nilsson A new type of receptor in the human retina

Extrafoveal retina from two human eyes which had to be enucleated because of peripheral choroidal melanomas was prepared for electron microscopy In both eyes the visual acuity was normal and the posterior pole of the eye was ophthalmoscopically normal Besides rods and conventional cones (cone 1) a second type of cone occurred much less frequently than cone 1 As compared to cone 1 it contained more stained

material in the myoid a greater concentration of neurotubules in the fiber and a much greater concentration of synaptic vesicles in the synaptic body In survey pictures these parts of cone 2 appeared substantially more electron dense than corresponding parts of cone 1 Whereas the cone 1 nuclei were lightly and evenly stained the cone 2 nuclei were speckled due to unevenly distributed chromatine Thus the two types of cones should be distinguished at low as well as at high magnification.

The differences between cone 1 and cone 2 are not unique for human retinal receptor cells Essentially the same differences were found between rods and cones in the frog Morphological characteristics of the kind described might reflect the rate of cellular activity If so cone 2 ought to be more active than cone 1 Ultrastructural differences might also accompany differences in photo pigment content and spectral sensitivity This is true for the red and green rods of the frog It remains to be seen whether the *same thing is valid for cone 1 and cone 2*

(This investigation was supported by a grant from the Swedish Medical Research Council Project no K/0 12x 734 04A)

T Svensson Indications for pre operative bacterial cultures from the conjunctiva in cataract surgery

J Cristiansson The tension in eyes after cataract surgery

Cataract operated patients were observed during their immediate postoperative ten days Applanation tonometry measurement of anterior chamber depth and noting the presence of hyphema or choroidal detachment were the main constituents of the study

There was a direct relation between a persistent low intraocular tension and hyphema and or choroidal detachment Anterior chamber depth was a less reliable measure than intraocular tension

A Anseth The importance of the corneal epithelium for the metabolism of the stromal cells

It has recently been reported that it is possible to replace the corneal epithelium with a contact lens attached to Bowman s membrane with adhesives The method may be c me beneficial in several corneal disorders but the question arises whether or not this procedure will affect the metabolic activity of the stromal cells The production of p lysaccharides (PS) reflects this activity and it is possible to localize and to a certain degree calculate the amount of PS by labelling with radioactive sulphate ($^{35}SO_4$) In the past several results based on isotope studies have been published the majority of which indicate that the presence of the epithelium is necessary for normal metabolic activity f the stromal cells The results however are not convincing because the methods used do n t reveal the specific activity of I S and consequently not the synthesis of it

The nly way to measure this synthes s is by isolating the pure PS fraction and meas u ng the is tope a t vity on it A method for the isolation and fractionating of the PS fr m rabb t cornea has been used in the present study In a series of rabb ts the epi thel al ells w re raped ff on one eye the fellow eye bein used as a control $^{35}SO_4$ was inj cte l in the anteri r chamber of both eyes and the rabbits were killed at dif f rent time pe iods aft r the injections The corneas were cut out and the isotope a tivitie in the is late l PS fractions were measured The results showed that the pec f c a t ty n the cornea without epithelium was considerably lower than in the ntr l rnea wh h in l cates that the epithelial cells are necessary for the synthesis of corneal I S Consequently one can suspect that a replacement of the ep thelium by an art f al lay uld be fatal for the underlying corneal str ma

A B H Sca n ng electron m c oscopy observat ns of Schlemm s canal

The canal of Schlemm in rhesus and vervet monkeys was opened in such a manner that relatively large areas of the inner and outer walls of the canal could be observed with the scanning electron microscope In many places the outer wall was hidden by perforated septa arranged longitudinally There were also tissue strands between the inner and outer walls of the canal The endothelial cells of the inner wall of the canal are long and slender with an average area towards the canal of 250 μ The nucleus of the endothelial cell and associated vacuoles bulge into the canal About 30 per cent of the cells have pores permitting flow of aqueous humor into the canal of Schlemm The diameter of the pores is 0 3 2 0 μ After erythrocytes had been perfused through the anterior chamber some red blood cells were recovered in the pores draining the aqueous into the canal of Schlemm

M Rydberg A case of acute keratoconus

H Bynke U Raunskov & L Aberg Calcium deposits in conjunctiva and cornea in patients with chronic renal failure

E Lindstedt Prenatal rubella infection as cause of visual impairment

Among 500 children with grave visual impairment 41 (8 per cent) had lost sight through prenatal rubella infection Most of the children had multiple handicaps in addition to visual impairment were hearing impairment mental retardation and or congenital heart disease

The visual impairment was grave caused by congenital cataracts Vision after operation did not exceed 0 1 in any of these children

It is important to combat prenatal rubella by prophylactic measures It is hoped that the practical difficulties of active immunization of young girls will be overcome in the near future

L Andersson Visual acuity as measured according to Monoyer Granstrom and by Titmus vision test – a comparison

A Alm Some aspects of the oxygen supply to the eye

The blood flow through the anterior superior ciliary vein in cats was collected after ligation of all other veins draining the uvea At normal intraocular pressure (IOP) and blood pressure this flow is very high 1 2 mL min and the arterio venous oxygen difference is low about 1 0 vol per cent This corresponds to an oxygen extraction of 8 μl NTP/min As the perfusion pressure defined as the mean arterial blood pressure less the IOP is stepwisely reduced through artificially increasing the IOP there is a reduction of blood flow The oxygen extraction per volume of blood is increased the total oxygen extraction remaining practically unchanged as long as the blood flow exceeds 0 3 0 5 mL min As for the oxygen supply of the uvea therefore the uvea itself is to a great extent independent of the amount of blood flowing through it

The oxygen tension in a tissue is determined by the oxygen content in arterial blood the oxygen consumption by the tissue and the blood flow through the tissue Determinations of pO in the vitreous close to the retinal surface have been made in cats using Beckman s micro oxygenelectrode Since the vitreous has no blood vessels and a low oxygen consumption pO close to the retinal surface may be taken as an estimate of pO in the retina

In the vitreous pO_2 within a distance of 3 7 mm from the optic disc and about 1 mm from the retina is normally 15 25 mm Hg Inhalation of pure oxygen gives an increase of the pO_2 This increase is highly variable ranging from only a few mm Hg to three times the initial value A change from pure oxygen to 6 5 per cent carbon dioxide in oxygen gives a marked rise of the pO_2 The same rise two to three times the initial

value, is also seen when changing from room air to 6 per cent carbon dioxide in room air

The effect of changes in the perfusion pressure on the pO_2 in the retina has been studied with the same method. Changes in perfusion pressure were induced as in the previous experiments by artificially increasing the IOP. The pO_2 in the vitreous close to the retina is largely unchanged until the perfusion pressure falls below 50-60 per cent of the initial level.

The effects of increasing the IOP on the pO_2 in the retina suggest an autoregulation of the retinal blood flow. The rises in pO_2 achieved by adding carbon dioxide to the respiratory gases suggest a mechanism of vasodilatation in the retina. It seems probable that the autoregulation of retinal blood flow is, at least in part, the result of the retinal vessels being sensitive to carbon dioxide.

Meeting in Stockholm Nov 28 1970

E. Linnér & W. Thorburn: Tonography at constant intraocular pressure

B. Porengren: Subretinal absorption of fluids and its importance for the clinical results of scleral buckling procedures for retinal detachment

The importance of the scleral buckling procedures in retinal detachment surgery largely consists of their ability to eliminate the retinal elevation, thus enabling chorioretinal contact. The mechanism of this effect is, however, somewhat obscure.

By studying cases of retinal detachment operated by injecting silicone into the vitreous it has been found that a continuous absorption of fluids from the subretinal space may take place. If this absorption theory is applied to scleral buckling procedures their effect becomes more easily comprehended.

The detrimental effect of the tear is its hampering of the pressure reducing action of subretinal absorption. Fluids from the vitreous pass through the tear, thus making the retina remain elevated. When a scleral buckle is applied over the tear this passage is eliminated, reducing the pressure in the subretinal space and making absorption possible.

I. Rendahl: Scotopic vision and traffic

B. Calissendorff & I. Rendahl: The clinical ERG in cases of night blindness

H. A. Hansson & T. Jerndahl: Ultrastructural studies of the development of the chamber angle in man.

S. E. Nilsson: Correlation of angiography and ERG in human retinal vascular obstructions.

Within a week after onset of symptoms six cases of central vein obstruction and four cases of central retinal artery obstruction were examined with fluorescein angiography and ERG (over a wide range of light intensities) in order to determine the retinal circulation time and the maximum *a* and *b* waves respectively. For comparison a normal material of 6 healthy eyes was used.

On the basis of the findings the pathological cases could be divided into two groups

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On the basis of the find ngs the pathological cases could be divided into two groups

1 *Successful cases* showing normal *a* and *b* waves and a mean retinal circulation time of 4 2 sec which means a moderate but statistically significant prolongation as compared to the normal cases (mean 2 2 sec) Evidently in these cases as judged from the ERG the circulatory obstruction was not severe enough to cause serious damage to the retina

2 *Unsuccessful cases* with a normal (in one case reduced) *a* wave but a markedly reduced *b* wave and a drastically prolonged retinal circulation time ranging from 7 to 350 sec Thus there was an obvious correlation between pronounced degree of obstruction and severe functional damage Whereas for the successful cases the decrease in visual acuity was to a great extent reversible the function of the unsuccessful cases remained very low

The results are being discussed in relation to the morphological basis of the different potentials of the ERG and in relation to new and promising attempts to treat central retinal vein thrombosis with an agent (Reptilase) inducing endogenous fibrinolysis ERG and angiography are used as a basis for selecting patients with reversible damage for such treatment Preliminary results to be published later indicate that patients on the borderline between successful and unsuccessful cases might be saved from falling into the latter group by means of early treatment with Reptilase

(This investigation was supported by the Swedish Medical Research Council Project K70 12x 734 04A and B71 12x 734 05B)

B Svedbergh Retrolental fibroplasia in Sweden 1960 1966

A Anseth & B Lindberg New aspects on the treatment of alkali burned corneas

B Philipson Biophysical studies of the reduction of lens transparency in cataract

The transparency of the normal young human lens is on the order of 90 per cent In cataract loss of light can be caused by resonance absorption and or light scattering The absorption is due to specific molecules which selectively absorb light in the visible wave length region Such pigment molecules are present in brown cataracts and constitute an insoluble fraction of the albuminoid However in most cataracts resonance absorption is an insignificant phenomenon and the reduced transparency must therefore be caused by scattering of light The sources of this scattering might be the protein molecules the subcellular structures the whole lens fibres and/or larger refractive interfaces

In order to elucidate the mechanism of the increased light scattering in cataractous lenses experimental cataracts in rats were studied X ray and galactose cataracts were analyzed by quantitative microradiography by light scattering analysis and by microspectrophotometry In the microradiograms sharp and wavy gradients of the protein concentration were found These gradients correspond to refractive interfaces which can explain the increased light scattering in these cataractous lenses

A number of human lenses with subcapsular cataracts have also been studied The distribution of protein was determined by quantitative microradiography revealing many similarities to those found in the experimental X ray cataracts The loss of transparency in these subcapsular membranous opacities is mainly caused by sharp and irregular gradients in the protein content The refractive index in the lens reflects the protein concentration Consequently light scattering in the human subcapsular cataract is caused by wavy refractive interfaces very similar to those in experimental X ray cataract

(This research was supported by the Swedish Medical Research Council Project B71 13x 5008 02B)

Robert C Drews Manual of Tonography C. V Mosby Co Saint Louis 1971 128 pages, 89 illustrations 12 appendices Price $ 13 5

The author s own wide experience in tonography and his skill in verbal presentation has resulted in a very good manual

The text is divided into four chapters history tonographic theory instrumentation and technique and clinical application An appendix contains tables for tonography and tonometry

Meticulous handling is a prerequisite in the tonographic procedure Technical equipment and its maintenance should be of the highest standard Tonography should be performed by trained personnel in order not to invalidate the results Without experience and knowledge of possible artifacts the tonograms could not be properly interpreted

Following the author s instructions tonography could maintain its position in glaucoma clinics – not least in control of the patients The author concludes his preface to deny patients tonography is to set glaucoma care back twenty years

P Brændstrup

W Starkiewicz Physiologische Grundlagen der Helligkeits und Farbenemfindungen Georg Thieme Leipzig 1970 198 pages 41 illustrations Price DM 37 00

The author Head of the Eye Department of the Medical Academy of Stettin Poland outlines present knowledge of two fundamentals of visual physiology – brightness and colour perception The survey mostly based upon literature studies shows some traces of the author s unorthodox philosophy

The didactic tripartition of the visual processes into an extrinsic physical world an *intrinsic physiological* event and an even more inherent *psychological process* may lead to dissenting opinions among scientists who are basically trained in disciplines not having very much in common because the basic concepts of phychology ordinarily are unfamiliar to physical and physiological ways of thinking

The author has created a new inclusive *term* the psycho physiological concept that may be refreshing for researchers accustomed to use either a physiological or a psychological reasoning In the author s opinion psychology can be meaningful to physiologists by a readoption of the theses of the old Pavlovian school Many psychological observations can be elucidated by using ideas as conditioned and unconditioned reflexes and inhibition and enhancement of physiological processes The author s enthusiasm for evolutionary theories and teleological explanations however tends to overtax this hypothesis a little

A chapter on photometry and the classifications of the terms luminance and brightness *could possibly be presented in a more didactic form* The sections on color perception first discuss the difficulties of fitting all neurophysiological and psychophysical evidences into either Young–Helmholtz s or Hering s classical color theories

Granit Schwactchan and Walraven made attempts to form a synthesis of the two theories not however on the receptor level but in the interganglionar switchboard The Dutchman Walraven supposed, for instance the following receptor signals R (R – C) (B thus assuming a four coded response from only three different recep

tors The author presents a new hypothesis claiming that integration of (B + G) is representing the missing fourth member of the code He endeavors to fit all known evidence into this theory

As an appendix, the last chapter of the book describes a device which conveys light to tactile stimuli to be perceived by the skin of the forehead of blind patients and emphasizes the practical importance of this aid for the blind

The book contains several original ideas and new concepts and can be an inspiration to further research It is of limited value as a text book on the subject but can easily be read by everybody interested in the topic

V Dreyer

Zagora Edwards Eye Injuries Charles C Thomas Springfield Ill USA 1970 601 pages Price $ 30 75

This handbook on eye injuries encompasses eye lesions of the broadest interpretation It not only gives a relevant discussion of the usual areas of concern such as mechanical chemical thermal electrical and ultrasonic lesions and their treatment but also provides an especially thorough and detailed review of neuro ophthalmological traumatology thereby giving the book an even wider perspective

This handsome book contains an abundance of illustrations which provide an excellent supplement to the text

It can be highly recommended for every eye surgeon and eye surgery department

Jens Edmund

Donaldson David D Atlas of external disease of the eye Vol III Cornea and sclera C V Mosby Co St Louis 1971 475 pages 254 figures and 112 stereoscopic views in full color on 16 VIEW MASTER® reels and a VIEW MASTER® compact viewer

This is the 3rd volume of the Atlas The first volume dealt with congenital anomalies and systematic diseases the second with the orbit lacrimal apparatus eyelids and conjunctiva

This atlas of corneal and scleral diseases is a very interesting book with beautiful stereoscopic slit lamp photos in full color and many interesting black and white photos in a text with detailed case histories

Cornea benefits more than any other ocular part from the 3 dimensional presentation Especially instructive are color pictures of dysgenesis mesodermalis of cornea corneal dystrophies Kayser Fleischers ring Fleischers ring in keratoconus posterior crocodile shagreen superior limbic keratitis intracorneal hemorrhage retrocorneal membrane epithelial cyst in camera anterior melanosis sclerae ochromosis scleromalacia perforans etc

Some of the slides could benefit from a greater magnification

The pictures are selected from 18 000 cornea stereographs compiled over a span of 21 years No wonder there are so many instructive pictures!

The format of this book basically resembles the Stereoscopic Atlas of Slit lamp Biomicroscopy by Braley Watzke Allen & Frazier (Acta Ophth 1971 49 173) the Stereoscopic Manual of the Ocular Fundus by Blodi Allen & Frazier (Acta Ophth

1971 49 172) and the Stereoscopic Atlas of Macular Diseases by J Donald M Gass (Acta Ophth 1971 49 510)

Donaldson's book of cornea diseases is to be recommended as an excellent stereoscopic atlas

M S Norn

The Fourth International Film Festival

organized by the Cercle de Médecine de l'Université Libre de Bruxelles *will take* place in Brussels 4–11 March 1972

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Ophthalmological Radiology
Radiology of the Eye the Orbit and Vision

A postgraduate course in ophthalmological radiology will be presented by Columbia University College of Physicians and Surgeons on Friday and Saturday April 21 and 22 1972 The Course will be directed to ophthalmologists and radiologists For further information please contact Dr Guy D Potter Columbia Presbyterian Medical Center 622 West 168th Street New York New York 10032

European Ophthalmic Pathology Society
Annual Meeting April 1971

A Joint Meeting of the European Ophthalmic Pathology Society (celebrating its 10th meeting) and the Verhoeff Society of America (celebrating its 25th anniversary) was held at the School of Pharmacy London England on 25th–28th April 1971 the scientific sessions being attended by 29 members of the E O P S and 25 members of the Verhoeff Society

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AUTHORS' INDEX

VARIA

The Fourth International Film Festival

organized by the Cercle de Médecine de l'Université Libre de Bruxelles will take place in Brussels 4–11 March 1972

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SUBJECT INDEX

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